Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

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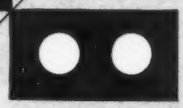

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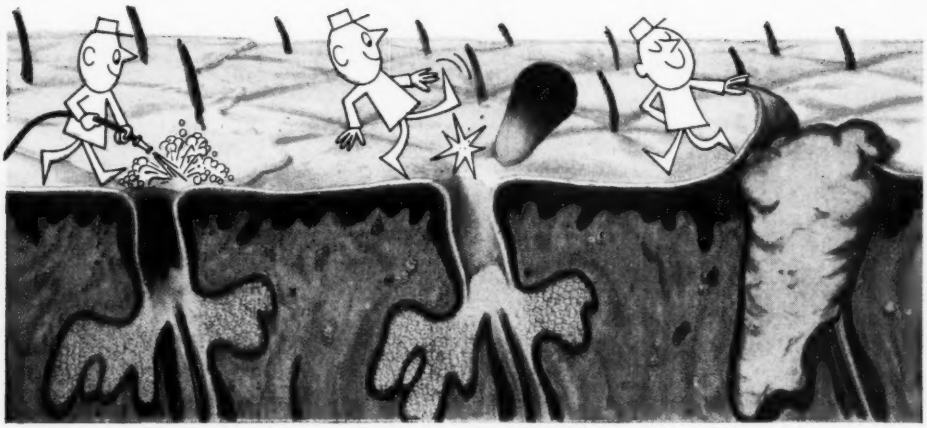

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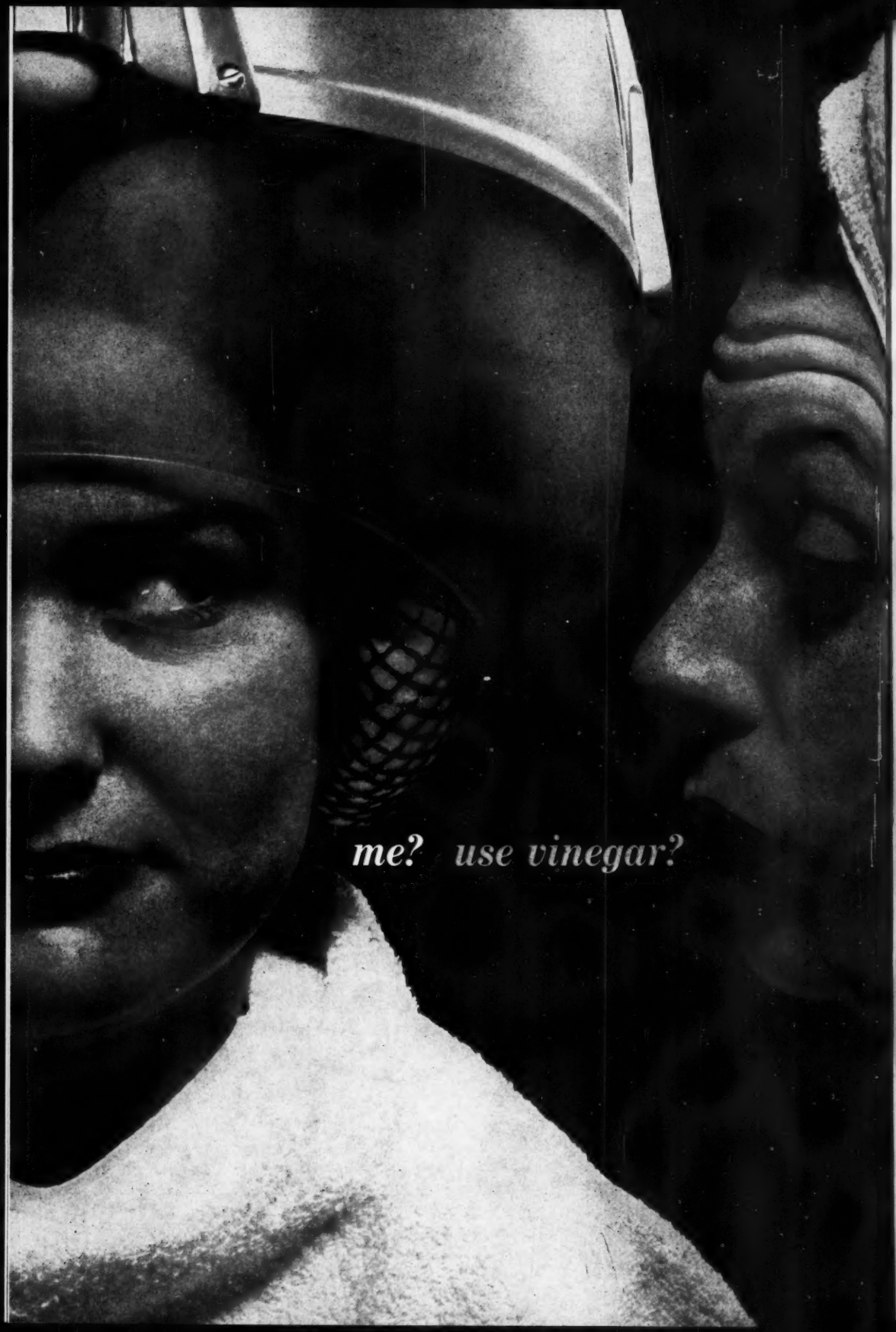
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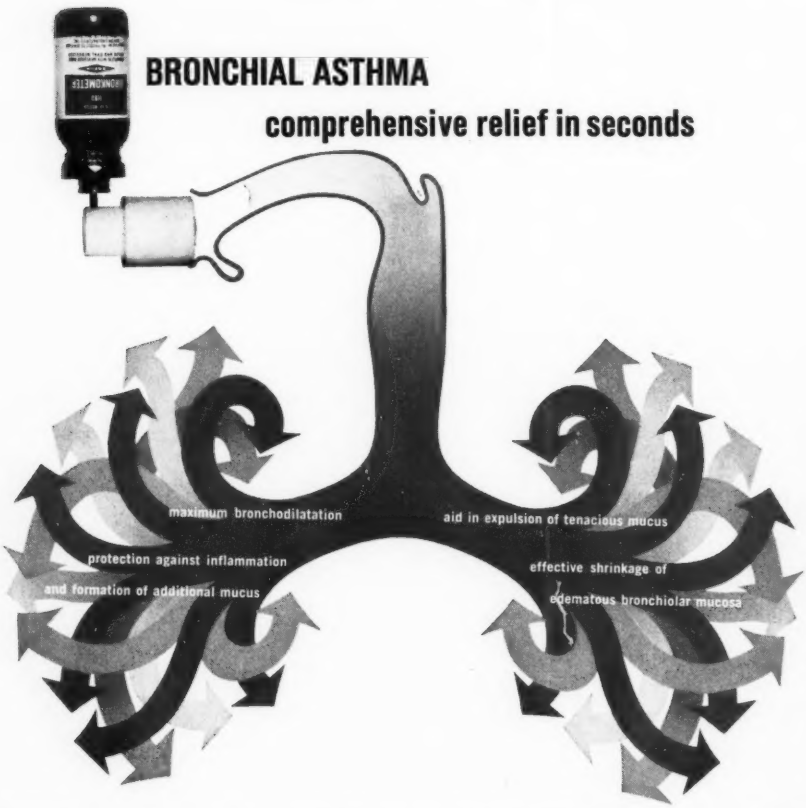

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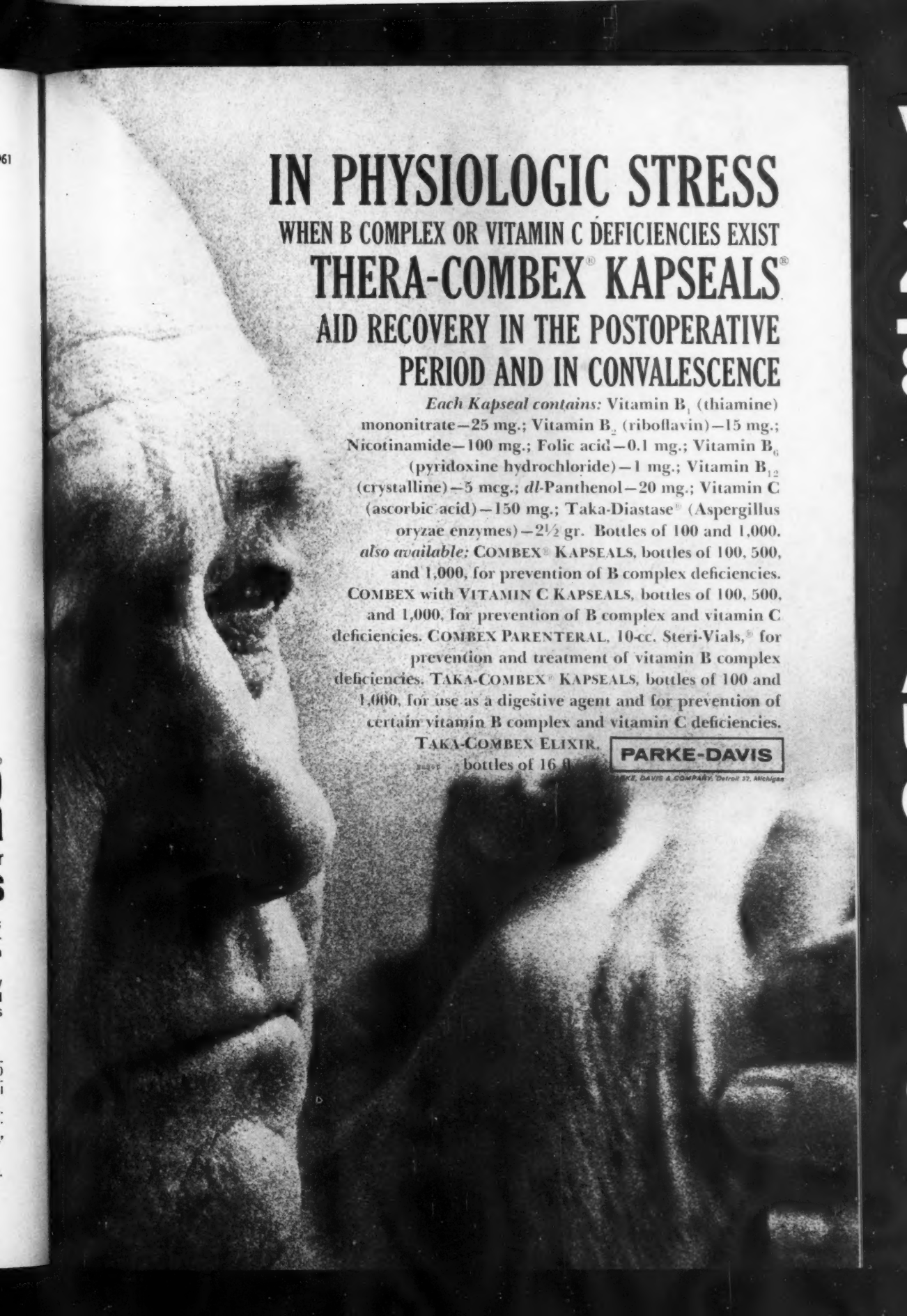
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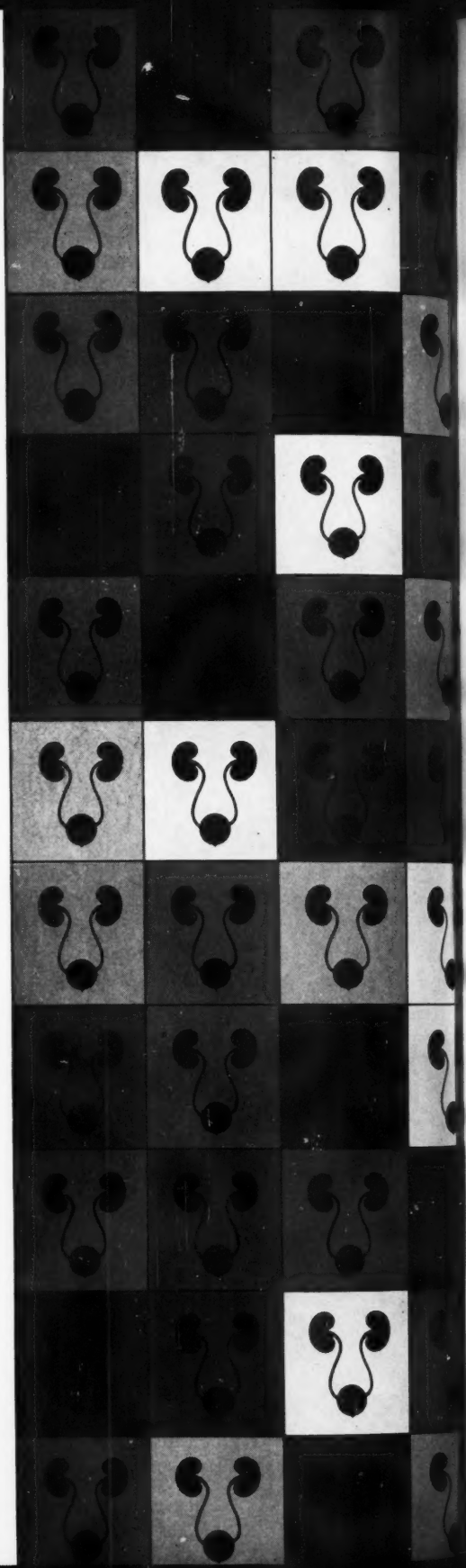

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Where infection remains latent due to causes which cannot be eliminated as in paraplegia, patients have been maintained symptom-free on dosage regimens ranging from 2 Gm. to 0.5 Gm./day. After initial control of acute symptoms, therapy may be continued indefinitely on a low dosage basis to guard against recurrence and prevent ascending infection. Many cases can be controlled with as little as 0.5 Gm./day.

SUPPLIED: No. 786 — "Thiosulfil" Forte — Each tablet contains sulfamethizole 0.5 Gm. (scored), in bottles of 100 and 1,000.

ALSO AVAILABLE — In urinary tract infection—to alleviate pain and control the infection: No. 783 — **"THIOSULFIL"®-A FORTE** combines the sulfonamide specific for urinary tract infection with a potent analgesic for prompt, soothing relief of local discomfort. Each tablet contains sulfamethizole 0.5 Gm. and phenylazo-diamino-pyridine HCl 50 mg., in bottles of 100 and 1,000 tablets.

References: 1. Bourque, J.-P., and Gauthier, G-E.: L'Union Medicale **89**:640 (May) 1960. 2. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. **56**:66 (Mar.) 1959. 3. Bourque, J.-P., and Joyal, J.: Canad. M.A.J. **68**:337 (Apr.) 1953. 4. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. **17**:320 (July) 1956.

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a new development in nonhormonal, anti-inflammatory therapy

more specific than steroids—
Acts directly on the inflammatory lesion **without** altering pituitary-adrenal function . . . **without** impairing immunity responses.[8-11]

more dependable than enzymes—
Rapid and complete absorption, without the uncertainty of oral or buccal enzyme therapy.[8]

more potent than salicylates—
Anti-inflammatory potency of Tandearil markedly superior to aspirin.[12]

Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis[1,2,3]; gout[1,4,5]; acute superficial thrombophlebitis[6,7]; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)[1,4]; severe forms of a variety of local inflammatory conditions[8,9,10].

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing. Full product information available on request.

Round, tan, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

References:
1. Graham, W.: Canad. M.A.J.: 82:1005 (May 14) 1960. 2. Vaughn, P. P.; Howell, D. S., and Klein, L. E.: Arth. and Rheumat. 2:215, 1959. 3. O'Reilly, R. J.: J. Irish M.A. 46:108, 1960. 4. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. 98:31, 1959. 5. Brodie, B. B., et al., in Contemporary Rheumatology 1956, p. 600. 6. Stein, I. D.: Ann. N. Y. Acad. Sc. 86:907 (March 30) 1960. 7. Barczyk, W., and Reb, W.: Praxis 48:589, 1960. 8. Miller, L. L., et al.: Proc. Soc. Exper. Biol. and Med. 87:358, 1954. 9. Rousselot, L. M.: Am. J. Surg. 97:429, 1959. 10. Summary of individual case histories submitted to Geigy. 11. Domenjoz, R.: Ann. N. Y. Acad. Sc. 86:203, 1960. 12. Smyth, C. J.: Ann. N. Y. Acad. Sc. 86:282, 1960.

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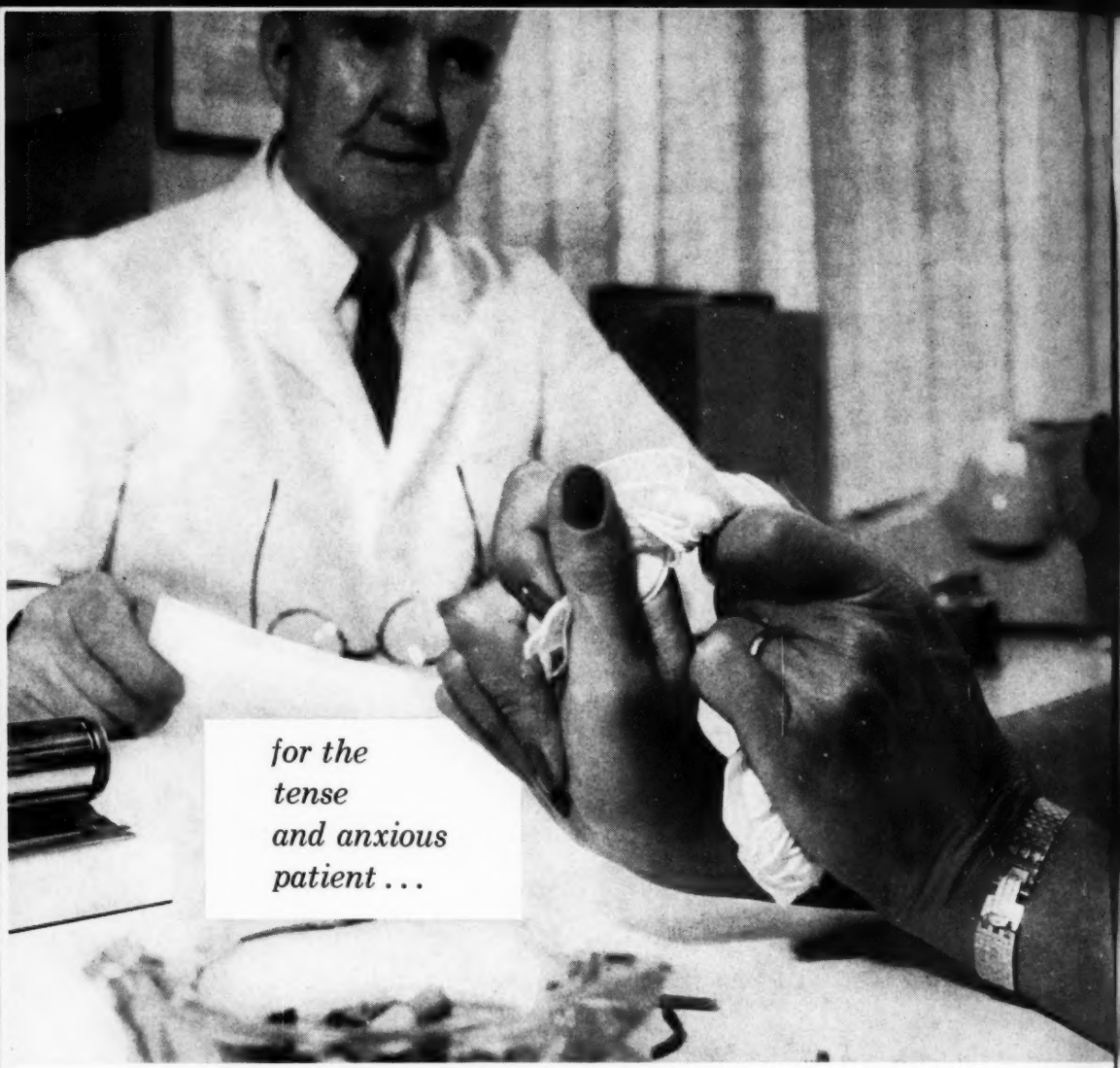

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Available: *Meprospan-400*, each blue-topped capsule contains 400 mg. Miltown (meprobamate). *Meprospan-200*, each yellow-topped capsule contains 200 mg. Miltown (meprobamate). Both potencies in bottles of 30.

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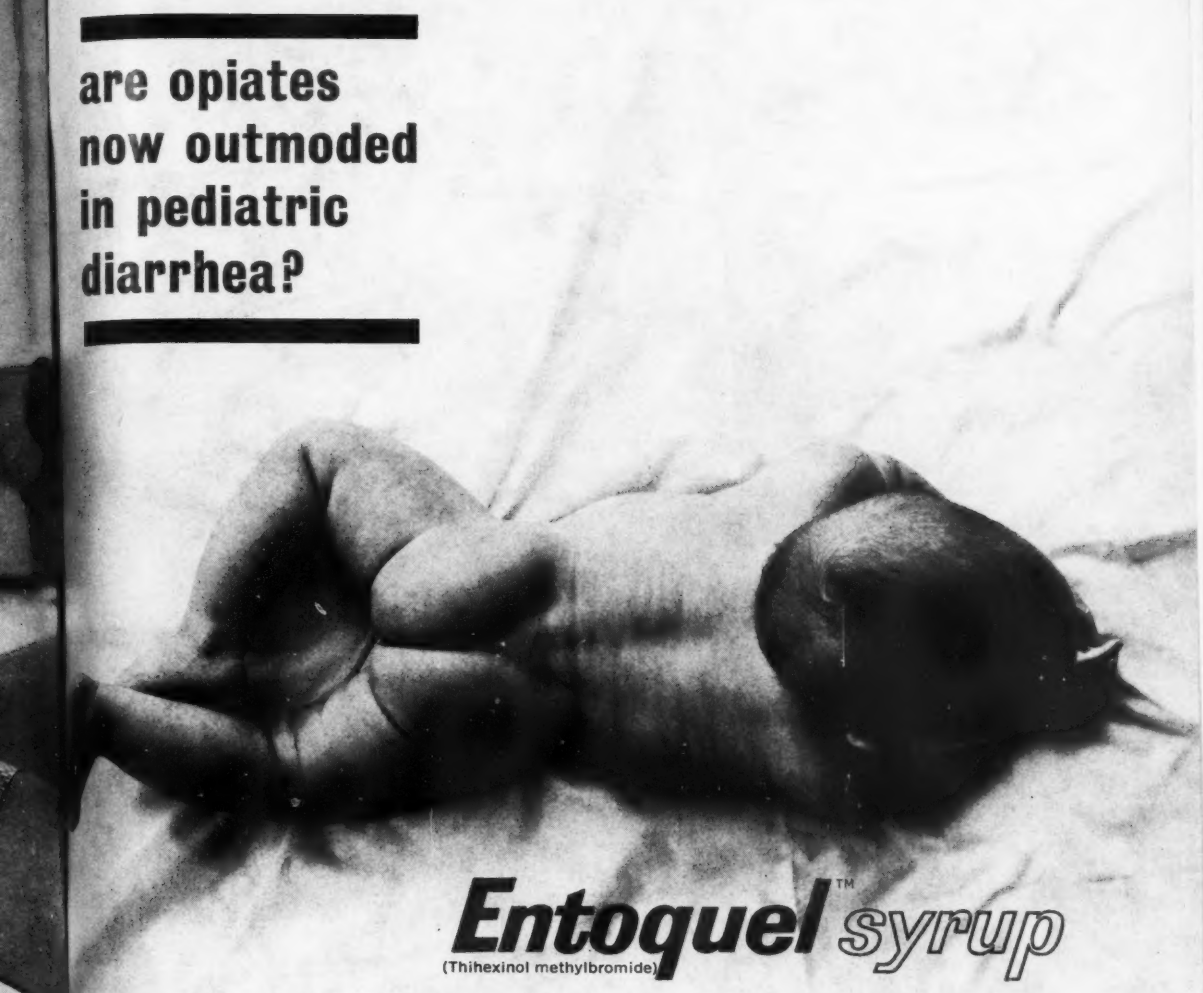
CMC-424P

are opiates now outmoded in pediatric diarrhea?



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AND WHEN THE DIARRHEA IS BACTERIAL IN ORIGIN

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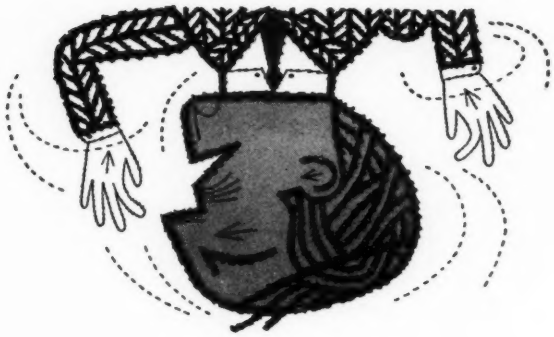

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Prescribe one ANTIVERT tablet (or 1-2 teaspoonfuls ANTIVERT syrup) 3 times daily, before each meal, for prompt relief of vertigo, Meniere's syndrome and allied disorders. Side effects are short-lived, usually only harmless flushing and tingling associated with vasodilation. As with all vasodilators, ANTIVERT is contraindicated in severe hypotension and hemorrhage.

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Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. 38:738 (Sept.) 1959.

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Larger volume per application assures total blockage of the cervical os and uniform coverage of the vaginal tract.

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Uniform dispersion of the proven spermicides[1] (in the surface of each bubble)... means the sperm is exposed immediately and constantly to spermicidal action.

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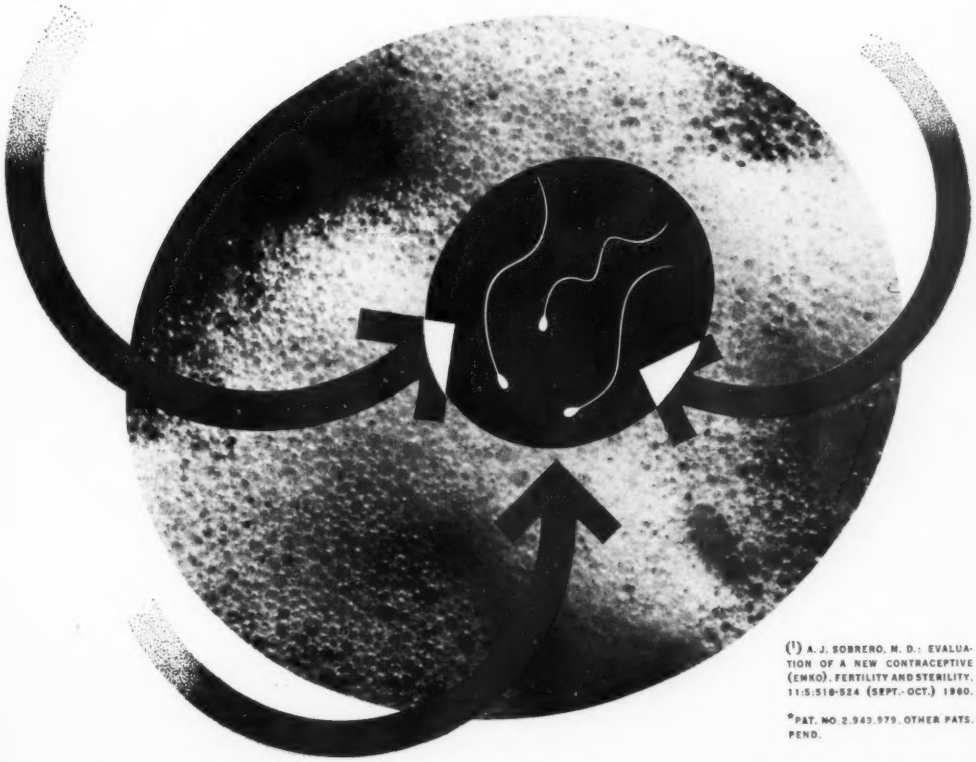
a principle never before applied to birth control...

FOAM



(1) A. J. SOBRERO, M. D.: EVALUATION OF A NEW CONTRACEPTIVE (EMKO). FERTILITY AND STERILITY. 11:5:518-524 (SEPT.-OCT.) 1960.

*PAT. NO. 2,943,979. OTHER PATS. PEND.

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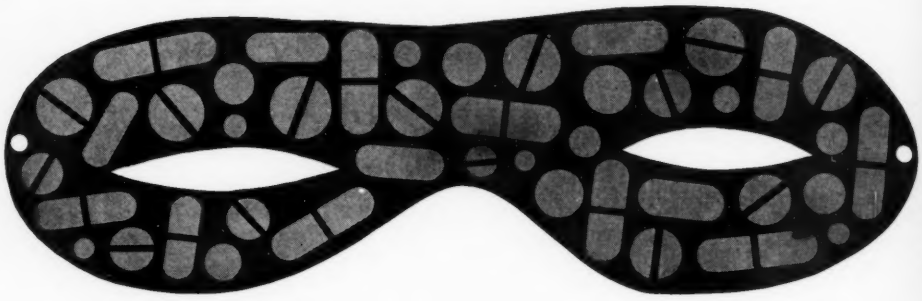

drugs anonymous

One of the several hastily conceived and potentially dangerous suggestions for reducing drug costs is generic-name prescribing. The proponents of generic-name prescribing claim that it will lower drug costs significantly and—through supervision by the Federal Government—provide quality equivalent to that of trademarked drugs. We maintain that these claims are false. Here are some authoritative answers to the principal questions posed by generic-name prescribing.

How much money would be saved if all prescriptions were written for generic-name drugs?

"The [Rhode Island] Division of Public Assistance examined 10,000 drug prescriptions for welfare recipients for the purpose of determining the actual savings . . . of generic versus trade-name drugs. The drugs had cost $28,000. Substituting generic drugs whenever possible would have provided a saving of less than 5 per cent. Syracuse has made a similar study of drug costs with comparable results."

Rhode Island Medical Journal,
January, 1961

Are the savings worth the risk of sacrificing quality?

". . . it is unsafe [to prescribe generically] because there is not sufficient policing of our standards. . . ."

Lloyd C. Miller, Ph. D.
Director of Revision of the U.S.P.

"The naive belief that, if a product was not good, the FDA would prohibit its sale is just not realistic. . . . it is completely impossible for the FDA to check every batch of every product of every manufacturer. . . . Hence the integrity and reputation of the manufacturer assume unusual significance where drugs and health products are concerned."

Albert H. Holland, M.D.
formerly Medical Director of the
Food and Drug Administration

Smith Kline & French Laboratories, Philadelphia

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Gantrisin

THE QUALITY OF GREATNESS

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Consult literature and dosage information, available upon request, before prescribing.

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the most effective anti-asthmatics...

administered in the most effective manner...

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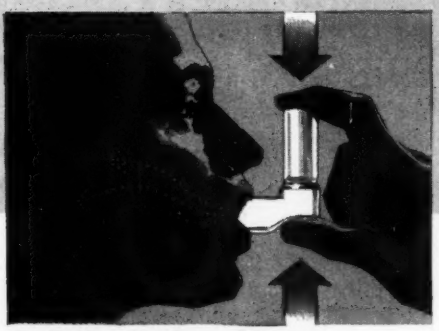

Available with either of the two outstanding bronchodilators

MEDIHALER-ISO®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.075 mg. isoproterenol.

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Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.15 mg. epinephrine.

Usual precautions for administration of isoproterenol and epinephrine should be observed.

Riker Northridge, California

3:439 Nov. 1951 Carroll G. & Brennan R. V. South. Med. & Surg. 113:352 Nov.

Where's the arthritic this morning?

Thanks to Medrol Medules, he woke up comfortable and he's already on the go.

The first long-acting oral steroid, Medrol Medules gives the arthritic patient therapeutic action that continues through the night. In many cases, morning stiffness can become a thing of the past.

The slow, steady release of methylprednisolone often provides greater effectiveness, with less frequent administration and sometimes a reduced total daily dosage.

Many of your arthritic patients, too, can wake up comfortable on Medrol Medules.

Dosage: The following dosages are recommended in rheumatoid arthritis:

	Initial	*Maintenance*
Severe	12 to 16 mg.	6 to 12 mg.
Moderately severe	8 to 10 mg.	4 to 8 mg.
Moderate	6 to 8 mg.	2 to 6 mg.
Children	6 to 10 mg.	2 to 8 mg.

With Medrol Medules, it may be possible to reduce the total daily dose by ⅓.

Indications and effects: Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications: Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief without developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

Approximately 135 tiny "doses" mean smoother steroid therapy

Each capsule contains: Medrol (methylprednisolone) 4 mg.
Supplied in bottles of 30 and 100.

Medrol* Medules*

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the urethra in postmenopausal urethritis: like "an electric wire with its insulation nearly worn off"*

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Suppositories

■ restores urethral "insulation" ■ prevents bacterial insult ■ relieves symptoms
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In more than 3000 patients, "over 90% have been relieved following treatment"*

Each FURESTROL Suppository contains diethylstilbestrol 0.0077% (0.1 mg.), FURACIN® (nitrofurazone) 0.2%, and diperodon HCl 2% in a water-dispersible base of glyceryl monolaurate and sorethytan (4) monostearate (Tween 61).

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Supplied: Box of 12, each 1.3 Gm. FURESTROL Suppository hermetically sealed in orchid foil.

*Youngblood, V.H.; Tomlin, E.M., and Williams, J.O.: Gynaecologia (Supp.) *149*:76 (Part 3) 1960.

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Entozyme also contains Pepsin, N.F., 250 mg., which facilitates the breakdown of protein.

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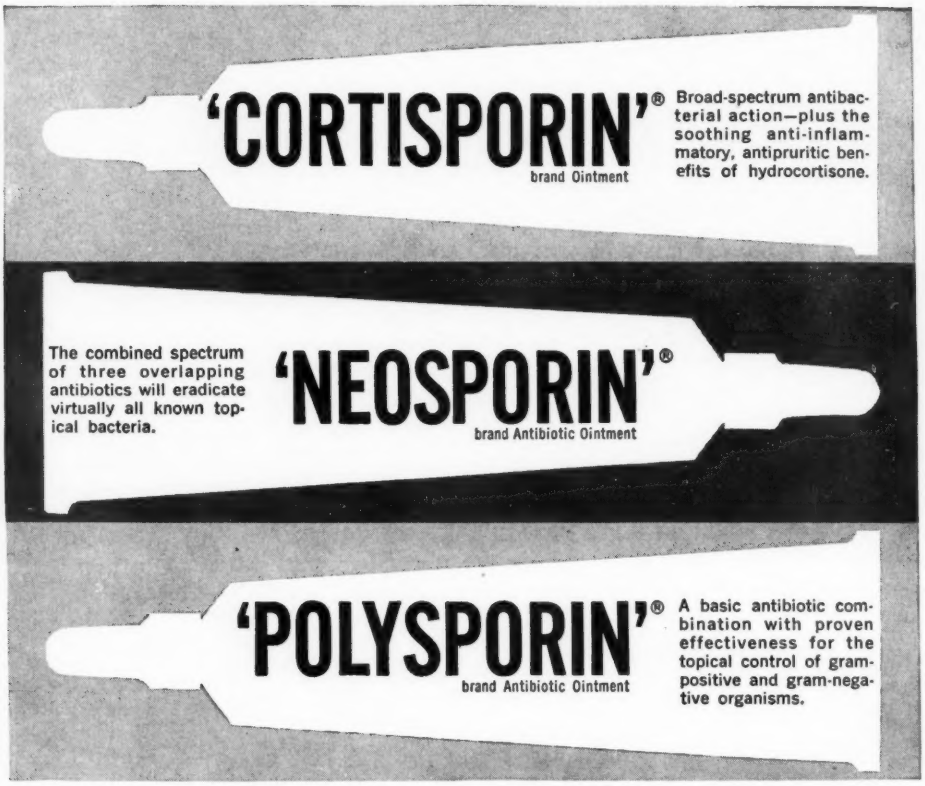
'B. W. & Co.' 'Sporin' Ointments rarely sensitize . . . give decisive bactericidal action for most every topical indication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Broad-spectrum antibacterial action—plus the soothing anti-inflammatory, antipruritic benefits of hydrocortisone.
The combined spectrum of three overlapping antibiotics will eradicate virtually all known topical bacteria.
'NEOSPORIN'®
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A basic antibiotic combination with proven effectiveness for the topical control of gram-positive and gram-negative organisms.

Contents per Gm.	'Polysporin'®	'Neosporin'®	'Cortisporin'®
'Aerosporin'® brand Polymyxin B Sulfate	10,000 Units	5,000 Units	5,000 Units
Zinc Bacitracin	500 Units	400 Units	400 Units
Neomycin Sulfate	—	5 mg.	5 mg.
Hydrocortisone	—	—	10 mg.
Supplied:	Tubes of 1 oz., ½ oz. and ⅛ oz. (with ophthalmic tip)	Tubes of 1 oz., ½ oz. and ⅛ oz. (with ophthalmic tip)	Tubes of ½ oz. and ⅛ oz. (with ophthalmic tip)

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When the Condition is not acute and diagnosis is not obvious

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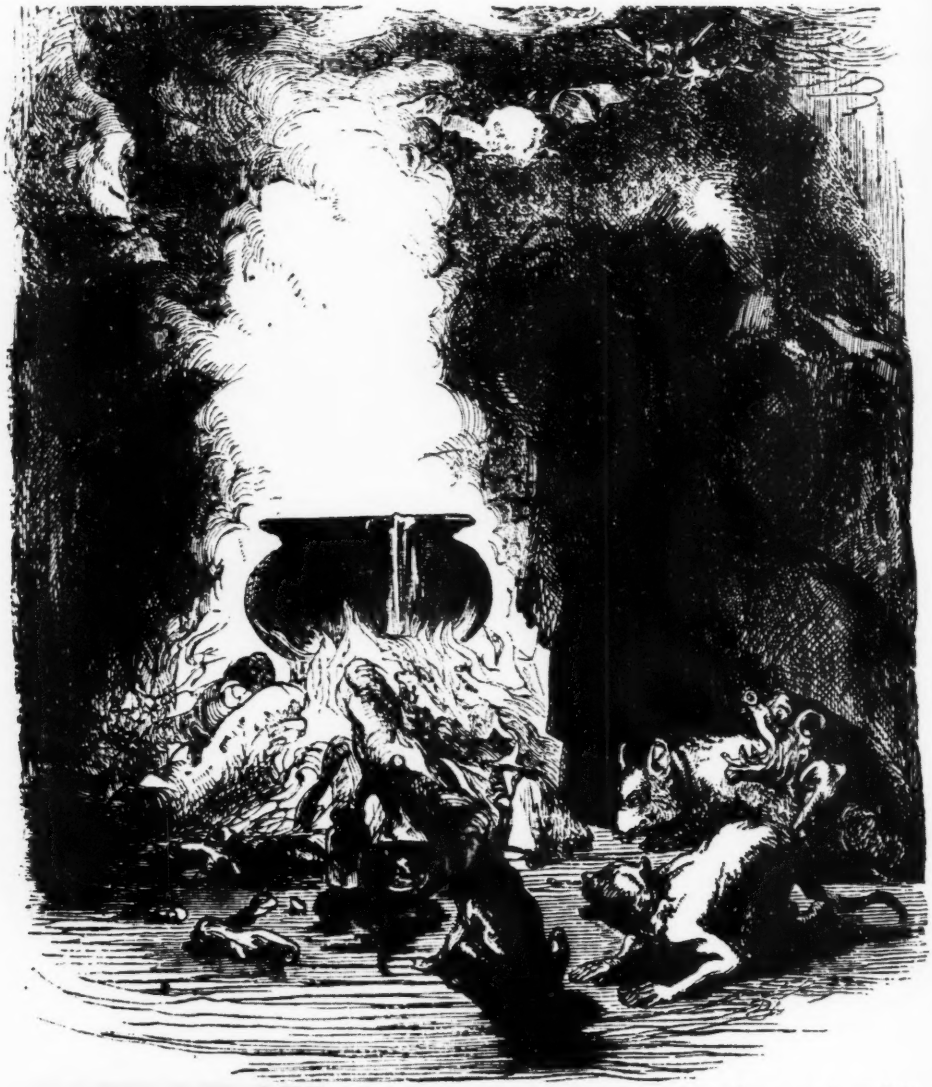

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Give immediate relief from heartburn and gastric distress with Al-Caroid. The fine-particle dispersion of balanced antacids in Al-Caroid quickly neutralizes excess gastric acid. The enzyme Caroid added to the Al-Caroid formula prevents interruption of protein digestion. When antacids raise the pH of stomach contents pepsin is inactivated, but the enzyme Caroid continues protein digestion in alkaline or acid media.

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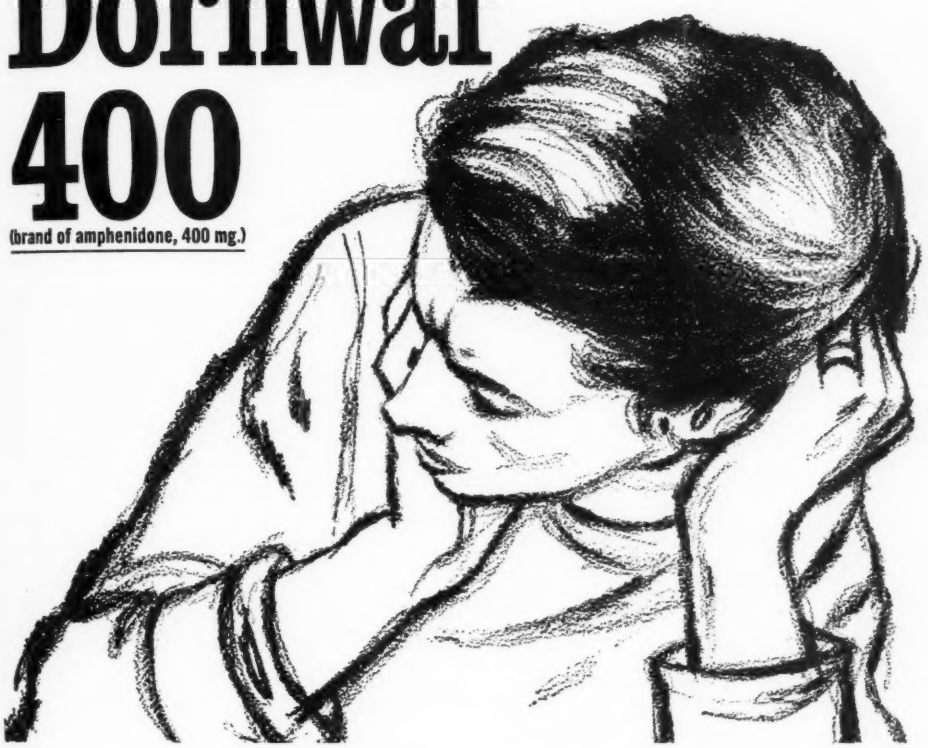
(brand of amphenidone, 400 mg.)



impressively effective against tension headache*

Dornwal 400 relaxes the musculature of the head and neck involved in tension headache and by doing so breaks the vicious cycle between psychological tension and muscular tension. Dornwal 400 also relieves anxiety and tension states quickly and effectively, usually without sedation or drowsiness. It is particularly suited to the active patient because it is relatively free from side effects such as depression and depersonalization. Some patients are relieved of their symptoms in as little as half an hour.

Dornwal 200 (amphenidone, 200 mg.), for similar conditions where lower dosage levels are adequate. Dornwal 100 (amphenidone, 100 mg.) is effective in the treatment of emotionally disturbed children.

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Wallace & Tiernan Inc., Belleville 9, N. J.

*Dixon, H. H.; Dickel, H. A., and Dixon, H. H., Jr.: "Clinical and Electromyographic Appraisal of Aminophenylpyridone," Northwest Med. 60:277 (March) 1961.

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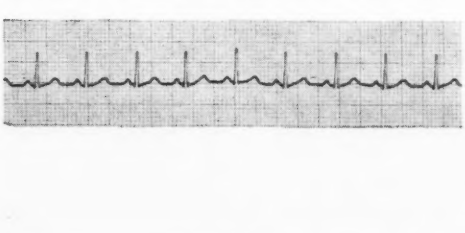

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Soma relieves stiffness —stops pain, too

YOUR CONCERN: Rapid relief from pain for your patient. Get him back to his normal activity, fast!

HOW SOMA HELPS: Soma provides direct pain relief while it relaxes muscle spasm.

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Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. **USUAL DOSAGE: 1 TABLET Q.I.D.**

The muscle relaxant with an independent pain-relieving action

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For restoring and stabilizing the intestinal flora

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Mixed culture of Lactobacillus acidophilus and bulgaricus with metabolic enzymes naturally produced.

TABLETS & GRANULES

For gastrointestinal disturbance diarrhea (antibiotic induced and others),[1] fever blisters and canker sores of herpet origin.[4]

Usual dosage for adults and childre Four tablets or one packet of granules chew and swallowed four times a day.

Supplied: Tablets in bottles of fifty—Granules in boxes of twelve one gram packets.

(1) Siver, Robert H.: Current Medical Digest, Vol. XXI, No. 9, Sept ber 1954. (2) McGivney, John: Texas State Journal of Medicine, Vol. No. 1, January 1955. (3) Frykman, Howard M.: Minnesota Medic Vol. 38, No. 1, January 1955. (4) Weekes, D. J.: N. Y. State Journa Medicine, Vol. 58, No. 16, August 1958.

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Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

August 1961

Symposium on Chronic Pyelonephritis*

Many years ago we spoke of pyelitis, a disease of young girls and of pregnant women especially. Clinical observations led to the evolution of the concept of pyelonephritis—a chronic disease which might cause secondary hypertension, and progressive loss of renal function to end in a uremic death. The correlation of these observations with the terminal pathologic findings at necropsy, and now intercurrent studies by renal biopsy, are rounding out thoughts concerning the pathogenesis of chronic pyelonephritis. Here is an infective process in which inflammation may run the gamut from low-grade reaction resulting in gradual scarring with ischemia and attendant impairment of renal function, to destructive or necrotic reaction and terminal sepsis. All information points to insidious, progressive and chronic disease which, when still more information is gathered, will certainly emphasize the need for the correction of contributing mechanical factors, for protracted observation and for prolonged antimicrobial therapy.

Pyelonephritis: The Natural History of Its Clinical and Histologic Spectra

GEORGE E. SCHREINER, M.D.,† *Washington, D. C.*

OUR TOPIC THIS MORNING is perhaps the most important a group of practicing physicians might be asked to consider. Various surveys have shown that from 6 to 20% of hospital patients have significant pyelonephritis shown at autopsy. This means that by the laws of statistics between 5 and 10 of the people sitting in this audience will have pyelonephritis.

We should have a clear definition of what we are talking about, and the simplest classification of pyelonephritis is one which has been in use for many years. Pyelonephritis is divided into acute, chronic or healed; atrophic or nonatrophic, based on the pathologic diagnosis; primary or secondary; urogenous, hematogenous or lymphogenous (Table 1).

The known causative factors in secondary pyelonephritis which will be considered in greater detail by the panel, are instrumentation, altered architecture of the nephron, extrarenal obstruction, pregnancy, diabetes, calculous disease, congenital anomaly, trauma and disorders of metabolism which affect re-

FIG. 1

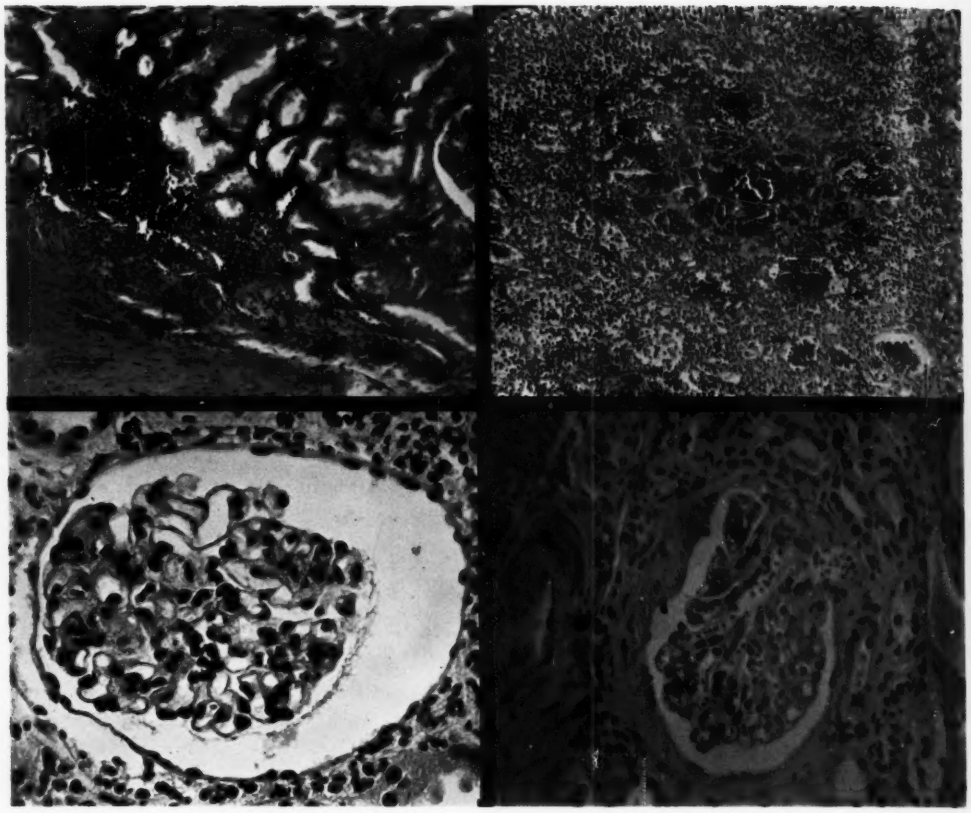
Girl 8 years old with pyelonephritis, enlarged spleen and hypertension.

*Presented before a Joint Session of the Sections on Medicine, Pathology and Urology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

The Symposium was co-sponsored by Eaton Laboratories, Division of The Norwich Pharmacal Company, Norwich, N. Y.

†Moderator of the Symposium, from the Department of Medicine and the Renal and Electrolyte Division, Georgetown University Hospital, Washington, D. C.

FIGS. 2-5



(Fig. 2, *upper left)* Subcapsular cortical inflammatory focus, in pregnancy and with increased blood pressure. (Fig. 3, *upper right)* Micro-abscess involving glomerulus in hematogenous pyelonephritis. (Fig. 4, *lower left)* Early inflammation with inflammatory cells in periglomerular lymphatics. (Fig. 5, *lower right)* More advanced inflammatory lesion with early fibrils outside Bowman's space.

sistance, which include disorders of gamma globulin, properdin, potassium deficiency, etc. (Table 2).

The most challenging thing about the problem of pyelonephritis is the fact that we are not diagnosing it (Table 3). Very recently Dr. Kleeman[1] has published a large series from the Wadsworth Veterans Hospital, showing that only 16% of 629 cases of chronic pyelonephritis were diagnosed before death. Through the clear vision of the "retrospectroscope," Dr. Kleeman examined the charts of these patients and found that in over half—I think he used the figure 70%—there was one clue which should have suggested to a suspicious physician the possibility of this diagnosis.

TABLE 1

CLASSIFICATION OF PYELONEPHRITIS

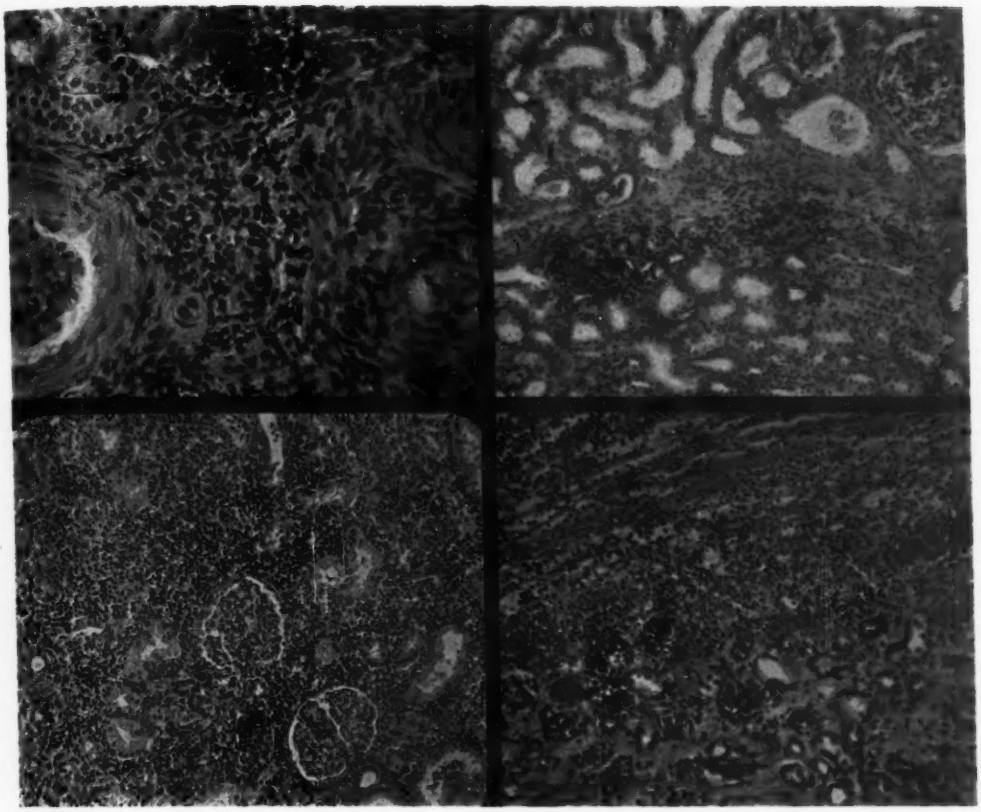
1. Acute, chronic, healed
2. Atrophic or nonatrophic
3. Uni- or bilateral
4. Primary or secondary
5. Urogenous, lymphogenous or hematogenous

TABLE 2

KNOWN ETIOLOGIC FACTORS IN SECONDARY PYELONEPHRITIS

1. Instrumentation
2. Altered architecture of the nephron (intrarenal obstruction)
3. Extrarenal obstruction
4. Pregnancy
5. Diabetes
6. Calculus or nephrocalcinosis
7. Congenital anomaly
8. Trauma
9. Hypogammaglobulinemia
10. Properdin deficiency
11. Defective general resistance
12. Foci of infection—a source of bacteremia.

FIGS. 6-9



(Fig. 6, *upper left)* Advanced periglomerular fibrosis with marked interstitial reaction. (Fig. 7, *upper right)* Partial recovery from pyelonephritis with toxemia of pregnancy, showing scar tissue. (Fig. 8, *lower left)* Interstitial spread of inflammation without localization. (Fig. 9, *lower right)* Medullary necrosis, the final stage of massive invasion from bacteremia.

Probably the largest single reason for the failure of our diagnostic batting average in pyelonephritis is a lack of understanding of the natural history of the disease. Since there is no single test that can give us the clue in every instance, we must understand this item.

How common is infection *per se* of the urinary tract? Again we have very little statistical knowledge, except from autopsy, of the incidence of tissue infection. Recent work, however, has shown the prevalence of infected urine in terms of bacterial counts. If we define significant bacteriuria as greater than 100,000 colonies per milliliter, then about 5% of male and 6% of female ambulatory outpatients, about 5% of male diabetics and 18% of female diabetics, between 12% and 30% of hospitalized patients, 11% of pregnant patients at term, 70% of patients hospitalized for genitourinary tract complaints, and 98% of patients who have an indwelling catheter for 4 days or more, have significant bacteriuria.

TABLE 3

ANTEMORTEM DIAGNOSIS OF PYELONEPHRITIS

Series	*No. Patients*	*%+*
Raaschou[2]	66	17
Likely[3]	22	22
Kleeman[1]	629	16.6

Some of the most important questions we may ask ourselves about pyelonephritis are: What are the causative agents? Are they always bacteria? Can they be viruses, fungi, yeasts, or other organisms? From where do they come? Do they come from endogenous sources, from foci of infection in the body, from the normal flora of the gastrointestinal or genitourinary tract? It has been shown that

catheterization for culture purposes may pick up bacteria from the urethra, and that cultures taken by needle aspiration from the bladder may give different results from those taken after distension of the urethra. Do these organisms travel via the blood stream, via lymphatics from the genital organs, many of which connect indirectly through the aortic chain with perforating lymphatics of the renal capsule, or do they mostly move by the ascending or urogenous route? What determines the susceptibility of kidneys in particular, to implantation by bacteria? We all have bacteremia; is it simply because the kidney receives a fifth of the cardiac output which makes it so susceptible, or are there inherent metabolic factors in renal tissue which make it a better organ for implantation? We know this is true in anomalies, in heredofamilial pyelonephritis, in hypo-immunity. We must also consider the problems that have been raised of the relationship of the ammonium ion to inhibition of complement; the problem of absence or presence of natural inhibitors in urine; the problems of obstruction and stasis of urine which contribute significantly to infection in the urologic patient. We must know metabolic factors, for example, low plasma potassium, deficiency in intracellular potassium particularly as it may relate to the renal tubular cell, diabetes mellitus, gout and nephrocalcinosis involving the renal parenchyma. What is the histologic spectrum of this disease? Why do some patients show localization of the inflammatory process, while others show interstitial spread? What is the clinical spectrum of the disease? Does pyelonephritis cause hypertension or vice versa? Does pyelonephritis account for a significant fraction of the toxemias of pregnancy and play a significant role in fetal mortality? Does pyelonephritis contribute to premature birth? Is chronic pyelonephritis a true infectious disease with living bacteria—always, sometimes or never? Our final question is: What is the best way to treat this disease? Obviously, we must understand the present theories of causation in order to manage this disease intelligently.

With this in mind, I shall answer only two of my questions. One is to give you a brief description of the clinical spectrum of pyelonephritis as we have observed it over the 10 year period the Renal Division has been in existence at Georgetown University (Table 4).

TABLE 4

THE CLINICAL SPECTRUM OF PYELONEPHRITIS (PN)

1. Asymptomatic
2. Healed
3. PN with labile hypertension
4. PN with congestive heart failure
5. PN with malignant hypertension
6. PN with encephalopathy
7. PN masking as toxemia of pregnancy
8. PN with necrotizing papillitis and anuria
9. PN resembling acute appendicitis
10. PN with localized peritonitis
11. PN with metastatic infection
12. PN with leukemoid reaction resembling leukemia
13. PN with urea splitter and stone formation
14. PN with nephrocalcinosis
15. PN with secondary hyperparathyroidism
16. PN with salt loss syndrome
17. PN complicating nephrotic syndrome
18. PN with amyloid nephrosis
19. PN presenting as gross hematuria
20. PN as pure gastrointestinal syndrome
21. PN with full uremic syndrome

The most important group of cases, from the standpoint of preventive medicine, is asymptomatic pyelonephritis, and it is usually true that a large percentage of patients with chronic pyelonephritis has no overt or distinguishing symptoms whatsoever. They may have general symptoms of malaise and fatigue. Healed pyelonephritics may show nothing except diminished renal size due to atrophy. One may see pyelonephritis with labile hypertension even in the very young; and one should suspect pyelonephritis when hypertension begins before 30 or after 50, because at these ages the onset of essential hypertension is extremely rare. We may see pyelonephritis presenting as a patient with congestive heart failure who can be improved by the treatment of infection. We may see it associated with malignant hypertension or with encephalopathy; we may see it masquerading as toxemia of pregnancy; and we may see the disease with anuria due to necrotizing papillitis or papillitis falling short of true tissue necrosis. We may see it resembling acute appendicitis; we may see it with localized peritonitis, particularly with perinephric abscesses or cortical collections of exudate underneath the peritoneal layer and producing local irritation. We may see it with metastatic infection,—in one year we had 5 pulmonary abscesses secondary to pyelonephritis. We may see pyelonephritis with a leukemoid reaction, and have seen white blood cell counts as high as 180,000 with this disease. We may see it with a urea-splitting infection such as Proteus, and with

stone formation; we may see it with nephrocalcinosis. We may see it particularly in the young age group with ureteral reflux and long-standing hydronephrosis and pyelonephritis.

Pyelonephritis may complicate the nephrotic syndrome or other intrinsic renal disease. We have 2 patients who apparently have secondary amyloid disease and in whom the only suppurative focus of infection over a long period was smoldering pyelonephritis. It may present as gross hematuria which in the elderly is easily mistaken for hypernephroma, as a pure gastrointestinal syndrome, or with any of the features of the full uremic syndrome.

An 8 year old girl (Fig. 1) was sent to us with a diagnosis of Wilms' tumor; the diastolic blood pressure was 160 mm. of mercury, and the systolic pressure was higher than the scale of the sphygmomanometer. Her urine showed only small clumps of glitter cells, which are cells damaged by association with tissue infection. Upon treatment with antibiotics, on the basis of this single urinary finding, the so-called tumor receded and proved to be a greatly enlarged spleen which is present in a significant number of children, particularly with pyelonephritis. Here we have the type of case in which it is hard to deny the association of pyelonephritis with severe hypertension, and certainly it would be difficult to call it coincidental for an 8 year old girl to have a diastolic blood pressure of 160 mm.

Now I should like to show very briefly some of the histologic spectrum of the disease, so one can visualize what is going on in the kidney. This biopsy material is from a woman who had an elevated blood pressure in the latter part of her pregnancy, and also had a subcapsular focus of inflammation high in the cortex (Fig. 2). Easily missed by biopsy, this may be the only finding in early, focal cortical pyelonephritis.

Here is hematogenous pyelonephritis with a micro-abscess involving the glomerulus which is destroyed in the center, and some interstitial spread into the periphery (Fig. 3).

Figure 4 shows early glomerular change. In the ring around Bowman's capsule, may be seen inflammatory cells in the periglomerular lymphatics, possibly the first sign of inflammation involving the glomerulus.

Next is a slightly more advanced lesion with early fibrils formed outside Bowman's space (Fig. 5).

Figure 6 shows far advanced periglomerular fibrosis with a massive interstitial reaction of histiocytes and inflammatory cells.

Figure 7 shows the findings in partial recovery. This tissue was from a woman who had toxemia of pregnancy associated with pyelonephritis; after delivery, renal function gradually improved and biopsy showed scars radiating from a delicate cortex through the kidney.

Figure 8 illustrates the type of case we worry about, one in which there is no localization of the inflammatory reaction but rather an interstitial spread.

The last figure shows the final stage of massive invasion, medullary necrosis, which may be fatal (Fig. 9). This case happens to be from a physician's brother who played golf on Friday and was dead with septicemia and medullary necrosis by Sunday night.

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Long-Term Control of Infection

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ONE DOES NOT HAVE TO BELABOR THE POINT that there has been dissatisfaction with the results of the treatment of chronic pyelonephritis. One can go back 25 years when the concept of the disease as we now know it was first established and accepted. At that time mandelic acid and later methenamine mandelate (Mandelamine) were introduced. Urol-

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ogists have devised various programs involving different numbers of days a patient was to be treated, varying dosages of drug, varying intake of water, variation of diet, all of which have been applied to this problem without outstanding success. The fact that people keep on searching for new answers to this problem means that everyone is dissatisfied. In 1948, the late Dr. Addis is said to have advocated continuous use of the sulfonamides in these patients, and this has almost certainly been tried by a number of physicians. One can find occasional records of patients who were kept on nitrofurantoin (Furadantin) for as long as 6 months or a year, in the early articles describing the use of this drug in the treatment of urinary tract infections. An organized attack on the problem of the effect of long-term administration of nitrofurantoin in chronic urinary tract infections was made by two pediatric urologists in Pittsburgh, Drs. Marshall and Harris,[1] who advocated continuous small maintenance doses of the drug in children and described good results in a third of 100 cases. Other papers also describe good results in occasional patients who are kept on nitrofurantoin for long periods of time. Grieble and Jackson[2] have carried a few patients on sulfamethoxypyridazine (Kynex) for up to 9 months. From the data in their article it is apparent that they were not really satisfied with what was accomplished.

Before the concept that the long-term administration of drugs does accomplish something in patients with pyelonephritis is widely accepted, I think it should be carefully examined. For instance, an article recently appeared from Norway in which a clinician in a straightforward manner advocates that all people with pyelonephritis should be carried on nitrofurantoin for a year.[3] This is a conclusion which cannot be endorsed at this time with the data now available.

The management of acute pyelonephritis is a relatively simple problem. Many chemotherapeutic agents and the combination of bed rest, antipyretics, high fluid intake and correction of urologic deformities will successfully handle acute infections in all except unusual circumstances.

The patients referred to in this study had established chronic urinary tract infections. They were referred to a special study clinic from the general clinics of the outpatient and inpatient services of the Medical Center Hospitals of the Medical College of South Carolina. All of the patients except one were indigent. Their course was followed only on an outpatient basis. Serial urine culture with return of organisms in large numbers were demanded before a patient was accepted for the study. The initial urine specimens were collected by catheterization. Thereafter, clean voided urines were obtained. The patients were carefully instructed but not supervised in the collection of the specimens. Organisms were enumerated by standard technics and cultural methods. Further evaluation included intravenous urography, urologic consultation when it was deemed necessary, careful pelvic examination, catheterization for residual urine or post-voiding cystograms as indicated, and evaluation of urinary function by endogenous creatinine clearance, urea clearance, 15 minute P.S.P. excretion, and multiple determinations at random for specific gravity. Nitrofurantoin, 50 mg. either 2 or 4 times a day, after a 4 day loading period of 200 to 300 mg. per day, and sulfadimethoxine (Madribon) 0.5 Gm. once or twice a day after one week on 1 Gm. per day, were the drugs employed in the study. At the very low dosage levels deliberately employed, there was no correlation between the urinary level of nitrofurantoin or the serum level of the sulfonamide on whether bacteria did or did not disappear from a given patient's urine.

Thirty-three patients were carried on nitrofurantoin for 3 months to 2 years, and 29 received sulfadimethoxine. Five patients who had not responded to nitrofurantoin were treated with sulfadimethoxine, and 4 patients who had not responded to sulfadimethoxine were treated with nitrofurantoin. In all 9 instances no patient responded to the change of drugs.

Forty-seven of the 62 treatment courses lasted over 6 months and 24 lasted over 12 months. Of the first 63 patients, 45 were negro females and 13 were white females. Four patients were male and all of these had some urologic abnormality.

Table 1 summarizes the treatment results in the 33 patients given nitrofurantoin. Bacteriologic response means that bacteria disappeared from the urine. In 17 the bacteria did not disappear from the urine, and 4 responded and then relapsed. It should be noted that symptomatic response may occur in the absence of bacteriologic response. The 12 pa-

TABLE 1

NITROFURANTOIN

		Symptomatic Response	*Sensitive Organism*	*Previous Drug Failure*
Bacterial response	12	10	12	0
No bacterial response	17	10	7	5
Response and relapse	4	4	4	0
Acute attacks during therapy	2			

tients who showed a bacteriologic response had an organism which was sensitive to nitrofurantoin in the urine initially. However, 7 of the 17 who did not respond also had a sensitive organism. Two of the patients had an acute attack while on therapy.

Table 2 summarizes the results of the 29 courses of treatment with sulfadimethoxine. There were but 8 bacteriologic responses and in 19 there was no response. Again, symptomatic response occurred in the absence of bacteriologic response. However, in contradistinction to the experience with nitrofurantoin, some patients who had an organism listed as resistant to sulfonamide in the beginning of the study responded bacteriologically. However, it should be pointed out that these resistances were determined on plates and not by serial tube dilutions.

From these data a few generalizations can be drawn. If a patient has not achieved a bacteriologic response in 3 weeks, he will not do so. There were 4 exceptions to this statement in the over-all group. If a urine remains sterile for 8 weeks, it will remain so if the patient is kept on a drug. Again, there were 4 exceptions to this statement. One should not conclude that these urines remained sterile only because the patients continued to receive the drugs. Some had possibly achieved true remission. In none of these cases was there a bacteriologic response after a patient had had a failure on the alternate drug.

Factors which tend to make pyelonephritis a more difficult disease to control are senility, the presence of diabetes, a stone in the urinary system, congestive heart failure, decreased renal function, hypertensive disease, pregnancy, a mechanical lesion of the upper or lower urinary tract, and mixed infections. The patients who did not achieve bacteriologic response averaged 3 of this list of complications whereas those patients who responded had only 2, as would be expected.

TABLE 2

SULFADIMETHOXINE

		Symptomatic Response	*Sensitive Organism*	*Previous Drug Failure*
Bacterial response	8	7	3	0
No bacterial response	19	11	5	3
Response and relapse	2	1	1	1
Acute attacks during therapy	7			

Characteristically, patients who do not respond have poorer renal function than those who do. It is interesting that in this group of 63 pyelonephritic patients, none was hospitalized in the 2 year period for pyelonephritis except the 3 who died: 1 of a cerebral vascular accident, 1 of congestive heart failure, and 1 of advancing uremia.

The major problem in evaluating this sort of clinical experience centers on how one decides who does and who does not have pyelonephritis and, second, by what criteria are individuals to be judged improved or not as a result of therapy. In this study, we have seen one woman who died of chronic pyelonephritis after 2 years of observation in the clinic. Urine cultures were done on an average of once monthly, and the urine remained sterile for the 2 years preceding her death until 6 weeks before her demise when an acute episode of pyelonephritis tipped her into uremia. Both grossly and histologically, her kidneys showed chronic, active pyelonephritis. One also sees patients who may have coliform organisms in the urine repeatedly for 3 or 4 months and then have them disappear spontaneously. One also sees patients who have fairly clear-cut pyelonephritis, as judged by clinical criteria, and who have both intermittent pyuria and bacteriuria. This is not a new observation. The intermittency of both the bacteriuria and pyuria of pyelonephritis was described at least 30 years ago.

The meaning of the suppression of bacteriuria is not clear-cut. A few patients in this study were maintained with sterile urines for periods of 6 to 18 months. They got along well during this time. When the drug was withdrawn, in 4 to 12 weeks the return of bacteria would be signaled by acute symptoms of upper or lower urinary tract infection. There is no evidence other than symptomatic to say that these patients have been improved by treatment. Serial biopsies were done in these individuals and histologically there was no change in the kidney. Also, serial functional studies were done and there was no improvement in renal function.

One also sees patients who do not have a remission of bacteriuria and who have a clear-cut symptomatic response. They gain weight, show an increase in level of hemoglobin, rarely have a fall in blood pressure if hypertensive, and have a diminution of symptomatology referred to the lower urinary tract. Yet in these individuals renal function and the histologic appearance of the kidney do not change either.

Thus, if we look at the criteria of renal function: blood urea nitrogen, blood pressure, degree of proteinuria and renal histologic findings, it is difficult to judge whether a patient has or has not been improved as a result of treatment with antibacterials. The exchange, "How are you feeling?"; "Much better, thank you, Doctor!," is not entirely satisfactory. Some individuals who give this response will be going "downhill" as you look at them. It would be a good idea for the clinicians working in this area to do what those interested in rheumatic fever have done. A set of rules by which the disease can be diagnosed and by which improvement can or cannot be judged should be drawn up.

Only one approach toward the problem of control of infection: continuous administration of drugs in small quantities, has been discussed. It should be stressed, moreover, that other approaches are being contemplated at this moment. Dr. Garvey and his colleagues have used a combination of a rapidly excreted sulfonamide and Mandelamine with encouraging results. Kass caused a flurry in the pyelonephritis world about 3 years ago when he advocated the use of large doses of hippuric acid to acidify the urine, but this flurry seems to have been stillborn and I have seen nothing published on it recently. Kass[4] has also advocated the use of high doses of methionine, which is excreted as a sulfate, to acidify the urine. It is useless in patients with poor renal function and requires the administration of up to 20 Gm. of the drug a day. For long-term purposes this is not good because many patients will not tolerate this amount. Seneca and Lattimer[5] have recently brought out the fact that chloromidron in small dosage will tend to inhibit the urease mechanism of urea-splitting organisms and thus make acidification of these urines easier. This is the development which should be watched with interest.

In conclusion, it can be said that chronic administration of antibacterials does have a place in the treatment of chronic pyelonephritis. Whether this significantly affects the over-all natural history of this disease in a given patient has not been established. Also, methods for establishing this are not yet apparent. Whether the disappearance of organisms from the urine represents simple suppression of bacteriologic growth and not a significant change in the urinary parenchymal flora has also not been established. Patients with resistant organisms, advanced chronic renal disease, and many complicating factors are less likely to respond than younger individuals who have no urologic lesion, good renal function, and no complicating factors.

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Obstruction, Instrumentation, Calculi and Their Effects on the Urinary Tract

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IT IS GENERALLY AGREED that obstructive lesions in the urinary tract are probably the most important predisposing factors to pyelonephritis. Obstruction at any level from the nephron to the urethral meatus can exert this influence. The type of lesion and the relative frequency of its occurrence vary with the age group. Examples are:

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(1) congenital anomalies in children
(2) tumor and prostatism in the old age group
(3) pregnancy in early adulthood
(4) calculi and other possible metabolic factors at all ages.

Functional obstruction, of course, also occurs in the absence of mechanical lesions. Examples are congenital neurogenic dysfunction and stasis, and acquired cord lesions with stasis.

Bell[1] found that obstructive pyelonephritis was 12 times more frequent than the nonobstructive type, and that infection was twice as common when the obstruction was in the bladder or urethra, as compared with urethral obstruction. He found that 60 to 70% of boys with resistant recurrent pyelonephritis had evidence of obstructive uropathy. This is not true in girls. Congenital valves do not occur often in the female urethra. The occurrence of infection in the lower urinary tract, however, is probably 10 to 1, at least, commoner in girls than in boys, even though obstruction of the vesical neck is rare in these cases. The incidence of ureteral reflux is about the same in boys and girls, in spite of the disparity in obstruction of the vesical neck, which makes the matter controversial as to whether this lesion is the common cause of ureteral reflux in children.

The mechanism of increased susceptibility to infection of a kidney with obstruction in the urinary tract is not thoroughly understood.

Congenital anomalies of the urinary tract, 40% of which occur in and around the kidney, and anomalies of the lower urinary tract are more common than malformations in any other system of the body. They comprise:

(a) Agenesis, aplasia, and general hypoplasia, partial hypoplasia (which is usually associated with ureteral duplication), focal hypoplasia or dysplasia. This latter includes primitive tubules, rudimentary glomeruli, excessive interstitial tissue (fetal kidney), medullary dysplasia and the common vascular abnormalities. Hypoplasia is a predisposing factor, but has to be differentiated from pyelonephritic atrophy which is the result of infection.

(b) Cystic disorders of the kidney, the most common of which is polycystic disease.

(c) The various anomalies of position, such as horseshoe kidney, crossed renal ectopias and other ectopic kidneys, most of which have drainage difficulties, many of which are due to incomplete rotation, and frequently occurring vascular anomalies.

(d) Hereditary interstitial pyelonephritis, which is a familial type of pyelonephritis in males which progresses to uremia and death.

(e) Intrinsic strictures at the ureteropelvic and ureterovesical junctions, diverticula of the ureter and congenital megaloureter.

(f) Bladder anomalies such as congenital diverticula, anomalous ureteral meatuses, bladder atony from imperfect innervation, congenital dilatation of the vesical neck in girls and congenital obstruction of the vesical neck from fibrosis and urethral valves.

(g) Congenital meatal stenosis.

Acquired obstructive factors in kidney infection that might predispose to the initial infection in pyelonephritis comprise tumors in any part of the urinary tract, stones, more commonly renal, obstruction of the vesical neck from benign hyperplasia, chronic fibrous prostatitis, carcinoma, and congenital valves in the male infant, urethral strictures, urethral and vesical diverticula both in the male and female, hypertrophy of the vesical neck in neurologic bladder lesions. There are, of course, obstructive lesions resulting from previous urinary tract infections that enhance recurrence and persistent infection of the kidney as well as the remainder of the urinary tract. And there is the occasional idiopathic periureteral fibrosis which obstructs and practically always produces pyelonephritis. Physiologic dilatation of the ureters in pregnancy predisposes to pyelonephritis. Toxemia of pregnancy with earlier ureteral dilatation and slower involution increases the incidence of pyelitis of pregnancy and postpartum pyelonephritis. As you know, Kass[2] found 8 to 10% of pregnant women to have significant bacteriuria, 40% of whom developed symptomatic pyelonephritis if untreated. He further found that if the patients were treated throughout pregnancy none developed pyelonephritis.

Vesicoureteral reflux in the presence of infection of the lower urinary tract is a common cause of pyelonephritis. Various figures are given of its incidence.

There is a question as to whether this does occur in the normal child as a congenital

thing or whether it may be acquired as a result of disease of the urinary tract. Apparently the length of the intramural ureter affects the incidence. It is well known that many early uropathies, such as infection of the ureteral meatus, obstruction of the vesical neck, and hypotonia of the sphincter in the presence of chronic cystitis will produce reflux. Another factor, which may or may not be obstructive and which predisposes to pyelonephritis, is urethrocystitis in the female. The short, straight urethra and the not too well-developed sphincter, the abnormal widening of the internal sphincter seen in a certain percentage of girls, plus the constant exposure to contamination from the rectum and vulva, account for the high incidence of infection of the lower urinary tract in the female. The high occurrence of vestigial para- and periurethral glands, involving the posterior urethra in the female, act as fertile soil for the perpetuation of infection in these areas. Not infrequently do we find fibrosis with contracture of the vesical neck resulting from long-standing infection in the female urethra. The same is true of the female infant wearing diapers bathed in urine and feces.

There is no doubt that the incidence of pyelonephritis is increased where patients with obstructive factors require indwelling catheters or need to have repeated instrumentation. The high incidence of infection in neurologic patients with bladder atony from retention, and in patients with stones and repeated manipulations of ureteral stones is well known to us all. Nosocomial infections in urologic wards where inlying catheters and poor sterilization technics have been used were quite common in the past; with better technic in the management of the catheters and sterile drainage apparatus, this has been reduced considerably in our practice.

The cause of calculous disease in general is not understood. The group caused by metabolic disturbances such as hyperparathyroidism, sarcoidosis, multiple myeloma, Burnett's syndrome, etc., and those secondary to virulent urinary tract infection, can be accounted for.

A third group, those with idiopathic calculous disease, may or may not be associated with infection or obstruction. It is possible that in all cases of urinary stone there is some alteration in the uro-epithelium which may predispose by lowering resistance to infection. Where a calculus produces obstruction, either in an infundibulum as in the ureteropelvic junction or in any part of the ureter, infection practically always ensues eventually. Once infection occurs in the presence of stone which acts as a foreign body, it can never be cleared until the stone is removed. The same is true of obstructive factors even in the absence of calculi at any point in the urinary tract. (There followed showing of several lantern slides illustrating types of obstruction.)

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Pyelonephritis Lenta and Its Relationship to Malignant Hypertension

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TODAY PATHOLOGY HAS CHANGED. The pathologist is no longer located in a little room in the basement of a hospital but is interested in clinical medicine. He is no longer merely fascinated by interesting slides or beautiful plasma cells, nor does he spend hours studying a peculiar tumor. The pathologist today has changed, just as pathology has evolved into a living science.

The pathologist is in constant contact with

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the clinician and the clinician does not accept the pathologist's word as final, but stresses "How do you know?" and "Why?" and often invites the pathologist to come and make rounds and urges him to participate in making a diagnosis at the bedside.

All in all, I wish to stress that whatever I am going to say is based not only on morphologic findings or on certain animal experiments, but also on observations of patients or on information about patients which is received in the Department of Pathology from young and astute clinicians.

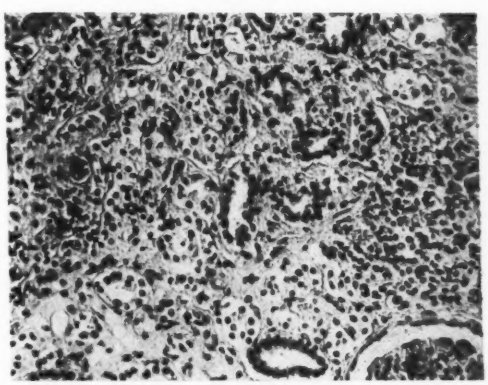
The concept of pyelonephritis, in general, has changed very much over the years. From our study it is obvious that there are two types of pyelonephritis. One form may present itself as a severe, so-called ascending infection of the kidney following severe cystitis. Such a kidney disease may cause suppuration of the pelvis with destruction of the pyramids and incorporation of the calyces into the pelvis. The cortex is also eventually affected, and gradually the kidney is so destroyed that no function is possible. This type of pyelonephritis is a destructive disease causing the kidney to be changed to a sac-like structure with pyonephritis or hydronephrosis. Since such a kidney may be severely damaged as a result of pyelonephritis, the disease may be designated as a destructive variety of pyelonephritis. Such a kidney may produce symptoms insofar as the infection is concerned and, if bilateral, renal failure is bound to ensue. This kind of kidney disease is not the topic of our discussion today.

There is another type of pyelonephritis which is a slowly developing disease with an insidious onset. It may be clinically silent for a long time. However, this form of pyelonephritis is extremely important because of its relation to hypertension. The patient may have developed the initial attack of pyelitis during pregnancy, or may have had past episodes of cystitis and pyelitis, or may not even remember previous attacks. These seemingly insignificant episodes of cystitis and pyelitis seem to heal very well. Because of the insidious onset and gradually developing disease in the kidney, which does not lead to destruction of this organ but which is extremely important in the pathogenesis of hypertension, this type pyelonephritis may be designated as "pyelonephritis lenta."

The starting point is an apparently insignificant infection of the urinary tract. Just how this infection proceeds from the bladder into the kidney I do not know. It may be a retrograde infection, it may spread along the lymphatics into the kidney, or it may spread by a hematogenous route from the bladder to the kidney. The primary lesion in the kidney itself is an inflammation in the true sense of the word involving the interstitial tissue and the tubular apparatus.

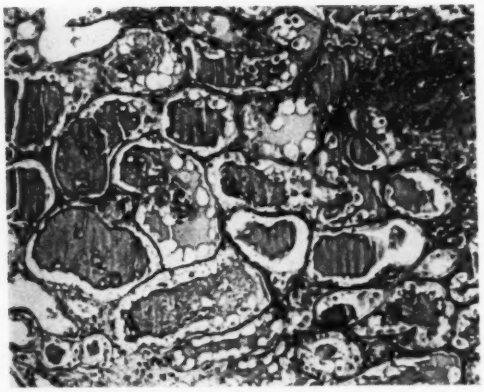
It is important to realize that most of the changes at first are found in the interstitial tissue and in the tubular apparatus (Fig. 1). Because of the involvement of the interstitial tissue, the disease may perhaps be designated as chronic interstitial nephritis. However, this term does not denote the source or origin of the lesion. Besides, this term in the past has been misused many times. The tubules are also markedly involved. They are either atrophic and surrounded by fibrous tissue with lymphocytic infiltrations, or they are dilated and contain a colloid-like material. The latter is often referred to as "thyroid-like" (Fig. 2). Up to this time the patient still may show only minor or few clinical findings referable to the kidney disease. However, the next step in the evolution of pyelonephritis lenta is of extreme importance. Within the interstitial tissue are located the arcuate and interlobar arteries. Any chronic inflammation close to a small artery anywhere in the body may cause secondary changes in the blood vessels. These changes are characterized by intimal fibrosis and eventual hyaliniza-

FIG. 1



Atrophy of tubules and slight infiltration of lymphocytes in pyelonephritis lenta. (H & E x 170.)

FIG. 2



Dilated tubules filled with a colloid-like material (so-called "thyroid-like" structure). (H & E x 105.)

tion, a process which is almost indistinguishable from arteriosclerosis (Fig. 3).

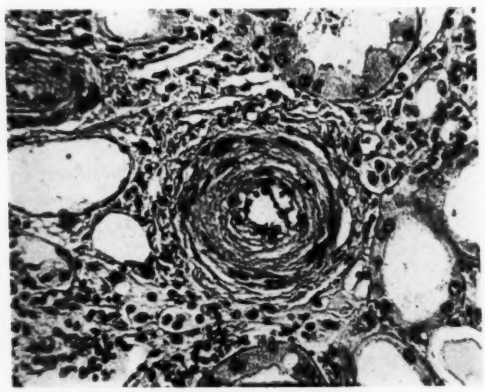
This intimal disease causes deformity of the arterial lumen combined with severe narrowing. If such changes occur in arteries elsewhere in the body nothing serious may happen, but if the lumens of the arcuate and interlobar arteries of the kidneys are severely narrowed renal ischemia is certain to result. At that stage the patient still may not show any clinical evidence whatsoever of renal involvement. However, depending upon the number of small blood vessels involved by narrowed lumens, the patient will gradually develop evidence of arterial hypertension. It is evident that this hypertension is comparable to the classic experiments where renal ischemia and hypertension are produced by the clamping of renal arteries. Since a patient with such kidney disease may, at the time, show little or no abnormality of the urine and no clinical evidence of renal involvement except for arterial hypertension, he may well be diagnosed as suffering from so-called essential hypertension.

Studying large necropsy series, we have found that the underlying cause of hypertension was often really this type of renal disease, the hypertension being the direct result of such a secondary involvement of many blood vessels. Because the renal disease itself may still be obscure, the term "lenta" with a connotation of "sneaky" seems justified. Nobody knows that there is an inflammation of the kidney which might have been present for a long period of time until the blood vessels are severely narrowed. Then the disease becomes manifest in the form of severe arterial hypertension.

The inflammation of the kidney, of course, goes on and causes more and more atrophy of tubules, dilatation of other tubules, and gradually also involves the glomeruli. The changes in the glomeruli are not at all of the type seen in acute or chronic glomerulonephritis. There is principally only fibrosis of Bowman's capsule (Fig. 4). The loops of the glomeruli are usually not affected.

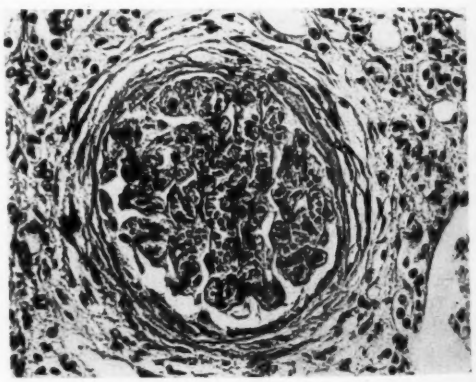
It is interesting, and there are various explanations for this, that the kidney, once the seat of an inflammation, may not rarely develop an acute attack of a similar disease. It is well known that a patient with chronic glomerulonephritis may get along well only

FIG. 3



Intimal fibrosis of interlobar artery (arteritis deformans) in pyelonephritis lenta. (H & E x 295.)

FIG. 4



Periglomerular fibrosis in pyelonephritis lenta. (H & E x 295.)

to die eventually in uremia. At necropsy not only may chronic glomerulonephritis be found but also an acute superimposed glomerulonephritis. In our material we have found the same to be true in patients who have pyelonephritis lenta. Some of these patients eventually die in uremia, the uremia being the result of an acute superimposed pyelonephritis. In other words, if a patient has pyelonephritis lenta he may get along well in spite of the fact that he develops a gradually rising systolic and diastolic blood pressure. However, such a patient may develop uremia following an acute superimposed pyelonephritis. The acute pyelonephritis is an additional factor which, superimposed upon pyelonephritis lenta, throws the patient into uremia. Such an additional superimposed factor is not necessarily only acute pyelonephritis, but may be acute glomerulonephritis or may even be impending myocardial failure. It may purely be the result of still more severe narrowing of the interlobar arcuate arteries of the kidneys to such a degree as to produce renal failure. This combination of symptoms—hypertension and rising urinary retention with changes in the eyegrounds—is characteristic of the malignant phase of hypertension. At autopsy such a kidney, because it was found in a patient diagnosed as having malignant hypertension, has been referred to and still is referred to as so-called malignant nephrosclerosis. We believe that malignant nephrosclerosis as a single entity does not exist, but that in the vast majority of cases the underlying kidney lesion in a patient who dies in malignant hypertension is that of chronic pyelonephritis lenta, of the type I have discussed, with a superimposed additional element which causes renal failure.

I do not like to be dogmatic, realizing full well that every pathologist becomes more set in his ways the older he grows, but I do want to emphasize again that there does not exist a single entity which may be called malignant nephrosclerosis. Let me repeat that in the majority of cases of malignant hypertension the autopsy will show the characteristic picture of pyelonephritis lenta plus an additional disease which is responsible for the occurrence of uremia. There are, of course, other diseases in the kidneys which may be found in patients who die of malignant hypertension, but these do not concern us today. But all these diseases, although different anatomically, have been thrown into one pot and have been named malignant nephrosclerosis.

I also wish to emphasize that much of the confusion that exists today concerning pyelonephritis is due to the fact that as a rule we do not differentiate two types of pyelonephritis. The destructive type of pyelonephritis which the urologist sees is an entirely different type of lesion than the one that I have discussed now—the one that I would like to term "pyelonephritis lenta."

Prevention and Care of Acute and Chronic Pyelonephritis in Children

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INFECTIONS OF THE URINARY TRACT in children are second only to infections of the respiratory tract in frequency, and therefore they present an imposing problem to those who are entrusted with the care of children suffering from renal diseases.

We have the good fortune to see on our Renal Service children as well as adults, and thus may survey the entire problem of chronic pyelonephritis from its beginning to the, unfortunately often, very unfortunate end.

In children two types of pyelonephritis can be much more clearly distinguished than in adults, namely acute pyelonephritis which was previously often called pyelitis, and a chronic smoldering form, called chronic pyelonephritis. It is generally recognized and well confirmed experimentally that urinary stasis due to ob-

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struction is one of the main causes of chronic pyelonephritis.

Since congenital anomalies of the urinary tract are very common—according to Campbell,[1] more than 10% of all humans are born with some urogenital anomaly and urogenital anomalies represent nearly 40% of all maldevelopments—any patient with persistent pyelonephritis must be subjected to a thorough search for the presence of congenital abnormalities with outflow difficulties. We have made it our rule in children to start a thorough medical, roentgenologic and urologic investigation of the urinary tract in any case of pyelonephritis which does not clear under suitable therapy within two weeks. The presence of chronic pyelonephritis in young children with stenosing lesions of the urinary outflow tract also serves to illustrate the point that chronic pyelonephritis often starts apparently from hematogenous sources; instrumentation was never carried out in these children before the discovery of their ailment.

In our children with chronic pyelonephritis the number of females was similar to Dr. Garvey's,—9 times that of males. One must not forget that the urethra in girls under 10 years is only 1 cm. in length at its best, and some females have such a short urethra that it is essentially only a urethral sphincter. In this respect some recent findings of Michie[2] appear to be of great importance. He placed 10 girls less than 10 years of age into a bath with dyed water, and found that all had dye in their bladder after they sat down and stood up 20 times in 6 inches of water.

The diagnosis of chronic pyelonephritis in children has become much easier since the poured plate method has come into use. The differentiation between an externally contaminated specimen and a really infected urine by means of colony counts has proved of great value in our hands, especially with the use of the so-called clean, midstream voided specimens. While the collection of such specimens in boys is not too difficult, the midstream voided specimens of girls are often badly contaminated and sufficient cooperation cannot be secured in the smaller ones. Here resort has to be taken to a small metal catheter. The use of a rubber catheter should be discouraged since it increases the chance of contamination by uncertain contact with the urethral orifice, especially in not very experienced hands. In agreement with Pryles and Steg,[3] we consider less than 100 colonies per ml. of urine as indicative of contamination, while urines containing more than 100,000 colonies per ml. are proof of a genuine urinary tract infection. The rare group in between requires re-examination which usually clears up the doubts.

Renal biopsies in pyelonephritis are informative only in approximately 60% of the cases. This is understandable because of the spotty distribution of the pyelonephritic microabscesses which may not be included in the biopsy. In addition, the performance of renal biopsies in small children is still a rather difficult procedure, since the target area is small and satisfactory cooperation of the patient can often not be obtained. The inability to produce concentrated urines is a common finding in children with advanced pyelonephritis. One may suggest that the swelling of the tubular epithelium and the infiltration of the medullary interstitium may prevent proper concentration of the urine by the countercurrent mechanism.

A word of warning should be said here against the all too ready decision to do a cystoscopy and retrograde pyelography in children. If *intravenous* pyelography is done within 30 hours after retrograde pyelography, 4 out of 30 children show hydro-ureters, probably due to swelling of the mucosa subsequent to instrumentation.[2] Since we consider obstruction of the outflow one of the leading causes for the onset of chronic pyelonephritis, especially in the presence of bacteria from the blood stream or in the urine, all such procedures should be considered very carefully before they are recommended.

Diagnostically, it can be stated that more than 50 white blood cells per cu. ml. in males and more than 100 in females in noncentrifuged specimens of morning urine, are found in most instances of pyelonephritis in children. Pyuria may, however, be temporarily absent in the presence of bacteriuria, especially in the early stages of the disease, when infection acquired by hematogenous spread, has not reached the tubular lumen as yet. In a considerable number of cases, especially with *advanced* pyelonephritis, erythrocytes can be found in large numbers, possibly due to erosion of medullary vessels. Occasionally, the differential diagnosis between pyelonephritis and glomerulonephritis may thus become a difficult one, especially in children. Here serum

complement (C^1) determinations may be of great help since C^1 is always low in acute glomerulonephritis but normal or high in pyelonephritis.

A final word should be said about the possible connection between renal hypoplasia, the so-called dwarf kidney, and chronic pyelonephritis in early life. Whereas there can be little doubt that some of these kidneys are due to failure of normal, fetal renal development, a rather considerable number must be attributed to pyelonephritis in infancy. This is indicated by the appearance of widely dilated tubules containing inspissated mucoid material, leading to the picture of struma tubuli as seen in outflow obstruction. In view of the significance of such kidneys, the necessity for an early diagnosis of chronic pyelonephritis in the child can hardly be over-emphasized.

Therapeutically, we like to select the medication according to the sensitivity of the microorganisms found. It should be stressed, however, that the drug thus selected must be given in *high* doses and for *prolonged* periods of time. The aim is eradication of the parenchymal or tubular infiltrating infection, and not only or mainly sterilization of the urine. In this respect, two unexpected findings have impressed us. Not too rarely, pyelonephritis can be cleared up by the prolonged use of very high doses of antibiotics against which the cultured organisms are only weakly or not at all sensitive. On the other hand, Furadantin (nitrofurantoin) seems to display good therapeutic effect, although therapeutic blood levels can practically never be established. We would like to speculate that the proven effectiveness of this drug may be due to sterilization of the urine in the tubuli with reduction of swelling therein. Thus the internal hydronephrosis ceases to exist, and the obstructive cause of pyelonephritis may be eliminated. This may also be the mechanism by which prolonged low dosage antibiotic therapy acts, once the main parenchymal foci are eradicated. One may also follow the ideas presented by Thompson and his group,[4] that Furadantin is reabsorbed in the distal tubuli and thus a much higher concentration of the drug may exist in the medullary interstitium, than can be expected from the blood levels.

In our experience, the treatment of chronic pyelonephritis in children offers a much better outlook than the treatment of this disease in adults, provided that obstruction is removed, wherever it plays a role.

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Response of the Connective Tissue and the Local Immune Reaction in the Kidney as Related to Pyelonephritis

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ALTHOUGH THE GENERAL HOST RESPONSES which arise to combat bacterial infections function in the kidney much as they do in other parts of the body, there are several features of urogenital infections which deserve special mention. My part in this discussion will be confined to the characteristics of bacteria and of reactions of kidney tissue which are important in the pathogenesis of pyelonephritis.

In table 1 are listed the types and frequency of organisms obtained from more than 1,000 consecutive positive cultures done in a large

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TABLE 1

FREQUENCY OF BACTERIA FOUND IN OVER 1,000 COLONIES PER ML. URINE[1]
(1,214 Studies)

Organism	*No. Strains*	*Percentage of Occurrence*	
A. aerogenes	269	22.1	22.5
A. cloacae	5	0.4	
E. coli	201	16.5	
E. freundii	15	1.2	20.2
E. intermedia	30	2.5	
Proteus sp.	218	18.0	
K. pneumoniae	39	3.2	21.2
Pseudomonas sp.	98	8.1	
A. faecalis	80	6.6	
S. aureus (coag. +)	34	2.8	
Other	225	18.6	

hospital clinic with an active genitourinary service.[1] In this table the value of 1,000 colonies per ml. of urine to denote a significant number of bacteria, rather than the commonly used value of more than 10,000 organisms per ml., was used because under the conditions in which this work was done procedural contamination in collecting clean voided specimens into sterile containers and prompt culturing did not exceed 1,000 organisms per ml. This table indicates that aerogenes, coli and Proteus families constituted approximately a fifth each of the positive cultures. Gram positive bacteria, chiefly staphylococci and enterococci, were much less commonly encountered even though many of these patients had received previous antibiotic treatment for urinary tract infections.

The striking implication of this compilation is that infections of the urinary tract most often are caused by organisms which inhabit the lower gastrointestinal tract and perineal surfaces. The characteristics of these bacteria are listed in table 2. These organisms are toxic once they invade tissue but are not invasive in the healthy individual. In general, humans do not have significant circulating antibody titers to these bacteria. Tissue invasion is controlled by the mucus barrier and lysozyme of the gastrointestinal tract and by the keratin layer and fatty acids of the skin.

Bacteria which do invade are promptly picked up by phagocytes, and because they are not virulent they are soon digested although they may circulate briefly inside of leukocytes while this destructive process is in process. In this respect we are all subjected to incidental sepsis which ordinarily is harmless. This type of sepsis is well controlled unless something happens to the leukocyte system to remove these cells as in agranulocytosis, or to inhibit their function as by excessive glucocorticoidal treatment. Under these latter circumstances the resident microflora of the skin and bowel may become invasive and establish focal infections in remote visceral locations.

In table 3 are listed some of the conditions which are known to be factors in establishing an experimental kidney infection. It is well known that different parts of the body are much better bacterial filters than others. When an experimental infusion of as much as 10,000 coliform organisms per ml. is given to an animal, it is found that the liver and the spleen are capable of clearing 85 to 90% of this number of bacteria on one passage through their vascular system. These studies are done with a cardiac-type cathether placed in the venous outflow tract from the organ under study. The lung is able to clear approximately 10% of the bacteria it receives and the kidney, like most other viscera not equipped with the rich reticuloendothelial system of the liver and spleen, clears even fewer bacteria.

In recent studies on small animals it has been found that as many as 10,000 coliform bacteria must be infused intravenously to establish infection in the kidney (Table 3). Once established, however, the infection progresses rapidly from the cortex, where the bacteria are first trapped, to the medulla of the kidneys where the few macrophages of the kidney are located. The features of this process are given in table 4. Even a small local infection in the kidney is slow to heal. When the kidneys are removed, ground up and plate cultures are made of the number of surviving bacteria at various stages in the evolution of an acute experimental pyelonephritis, it is

TABLE 2

CHARACTERISTICS OF URINARY TRACT PATHOGENS

1. Resident flora of gastrointestinal tract
2. Low virulence
3. Toxic by virtue of endo- and exotoxins
4. Extracellular parasites
5. Induce little or no immunity except by overt infection or as result of pyogenic infection

TABLE 3

PREDISPOSING FACTORS—HEMATOGENOUS INFECTION

1. 10,000 organisms i.v. to establish infection
2. 10 organisms in kidney—infection
3. Initial infection cortical—spreads to medulla in 48 hours
4. Trauma or obstruction plus sepsis = pyelonephritis
   (a) Renal massage
   (b) Local cautery
   (c) Ureteral, lymphatic or venous obstruction

TABLE 4

PREDISPOSING FACTORS WITHIN KIDNEY

1. Minimal phagocytic endothelial system—few macrophages in medulla
2. Without predisposing factors, tissues not sterilized for 1 to 2 weeks
3. With predisposing factors, organisms persist
   (a) Coliform bacteria for 4 to 6 weeks
   (b) Enterococci, staphylococci for months

found that viable organisms persist for from one to two weeks. When fluorescent antibodies directed against antigens in these bacteria are used to determine how long bacterial products persist after infection, it is found that these residues remain for 4 to 6 weeks even though evidence of infection may have disappeared from the urine long before this time. Enterococci and staphylococci are known to persist for even longer periods of time in renal tissue. The doctor who treats an acute kidney infection should keep this in mind as he plans antimicrobial treatment.

The role of mechanical factors in the pathogenesis of pyelonephritis has been stressed by other speakers on this program. These factors are listed in table 5.

In animal studies, obstruction of the lower urinary tract has been shown to promote ascending infection via the urine column to the kidney; and where there are disordered ureteral or bladder dynamics, a migration of carbon particles as well as bacteria has been traced through the lymphatics to the kidney as well. Various changes within the kidney itself may have a similar mechanical obstructive function. Renal massage during experimental sepsis, for example, has been widely used to establish experimental pyelonephritis. Even local cautery of a small portion of the renal cortex will set up microscopic obstructive changes which promote an infection. Since these types of intrarenal obstruction are soon masked by a spreading infection, it is not surprising that pyelography and other procedures available to the urologist often do not give evidence of obstruction as a factor in human pyelonephritis when there may well have been an obstruction.

TABLE 5

PREDISPOSING FACTORS—ASCENDING INFECTION

1. Congenital deformities, polycystic disease
2. Pregnancy
   (a) Bladder atony
   (b) Ureteral dilatation, endothelial hyperplasia
   (c) Puerperium—submucosal hemorrhage, edema of bladder trigone
3. Spinal cord injury or tumor
4. Advancing age—prostatic hypertrophy, cancer of the cervix, etc.
5. Retrograde lymph flow above ureter at pressures above 70 cm. water

In the pyelonephritis of pregnancy atony and physiologic obstruction may be a similar, unapparent form of obstruction. It also should be noted that transient obstruction for several hours can establish experimental infection which otherwise would not have occurred. Pyelography will rarely detect this state of affairs.

One of the most interesting recent developments in the pathogenesis of kidney infections has come from the group working with Paul Beeson[2] at Yale Medical School. These workers, noting the ease with which infection can be established in the kidneys as compared to the liver, suspected that there might be a tissue inhibitor which interfered with immune mechanisms. Table 6 outlines the essentials of this system. These investigators studied kidney extracts, and found that dilutions of extract did indeed block the bactericidal power of specific immune serum. These observations led to other studies which eventually demonstrated that ammonia released by kidney tissue blocked the fourth component of complement. Since complement is necessary for the bactericidal power of serum, this action is explained in table 7. Others have since shown that the urea splitting activity of bacteria, Proteus in particular and other coliform organisms as well, plays a part in this reduced bactericidal power of renal tissue. The renal tubular cell is rich in glutaminase activity.

TABLE 6

PREDISPOSING BIOCHEMICAL FACTORS

Kidney tissue extract 1:8 inhibits bactericidal power of antibodies:
   (a) NH_4 at alkaline pH blocks 4th component of complement (C_4)
   C_4 necessary for antibacterial function of serum
Kidney glutaminase activity rises with NH_3 release:
   In first 2 to 5 days of NH_4Cl therapy (i.v. *E. coli* = 80% pyelonephritis)
   (b) In K deficiency (predisposes to pyelonephritis)
   (c) In starvation (i.v. *E. coli* = 35 to 40% pyelonephritis)
   Therapy with NH_4 acetate, urea = no effect

TABLE 7

PREDISPOSING BIOCHEMICAL FACTORS

Proteus sp. will grow both in and outside tubular cells:
   (a) at 100 mg./100 ml. urea NH_3 released locally,
   (b) at pH 8 epithelial cells killed in 8 hours,
   (c) $Mg.NH_4.PO_4$ microstones formed.

Tissue cultures of these cells are readily infected. *Proteus sp.*, for example, will grow intracellularly. When the urea content in the media is adjusted to physiologic levels occurring in the normal kidney, it is split intracellularly. Cells die after several hours exposure to a pH of 8 brought about by the ammonia released. The formation of magnesium-ammonium-phosphate-crystals in Proteus infections is thought to come about by this means.

Another aspect of these interesting studies is the finding that conditions which increase glutaminase activity, such as the administration of ammonium chloride or low potassium levels, also will act as adjuvants in establishing a renal infection. In this system ammonium chloride, administered at the same time that an intravenous infusion of a subinfectious dose of bacteria is in progress, will establish pyelonephritis.

In table 8 are given some of the immunologic aspects of experimental pyelonephritis.

In the type of infections we have just described, a brisk antibody response develops to the specific bacterium causing the infection. When an animal which has recovered is again subjected to sepsis and trauma, using the same bacterial species, no pyelonephritis develops. In other words, solid systemic immunity is quite adequate to protect the kidney. It is very likely the same situation applies to human kidney infections and it is for this reason that most human renal infections are self limited even without antibiotic treatment.

In some patients recurrent or persisting pyelonephritis occurs and it is this group of patients which is the problem for the urologist and the internist. We do not know what happens to the immune responses in these people or whether the recurrences are caused by the same or antigenically different bacteria. The chronicity of their illnesses suggest that there may be some other immunologic factor at work.

TABLE 8

IMMUNE AND HYPERSENSITIVITY PHENOMENA

1. Renal massage + sepsis = PN, immunity, recovery
   Renal massage + sepsis (same strain) = no PN, recovery
2. Local vaccine—interval—sepsis (same strain)
   (a) Live vaccine—hypersensitivity reaction = PN
   (b) Dead vaccine—hypersensitivity reaction = PN
3. Fluorescent antigamma globulin
   (a) Localizes at sites of lesions in lupus, glomerulonephritis, periarteritis

PN = pyelonephritis

Thelen,[3] in Germany, recently has searched for allergic mechanisms in kidney infections. He made local innoculations of living or dead bacterial vaccines into the kidney tissue. As a result, the animals developed an allergic capacity to react locally to these organisms. Both gram-negative and gram-positive bacteria were studied. When the animal so sensitized was then submitted to sepsis, using a bacterial strain isologous to that used for the first innoculation, he obtained a local flare-up of pyelonephritis. It appears that the ability of the bacteria to cause greater local injury than they would normally cause, by virtue of bacterial allergy superimposed on their direct toxic activity, was the mechanism of this effect. In this respect the injury caused by allergy was like the mechanical effect of local cautery in establishing local infection.

Recent interest in auto-immune disorders has encouraged the search for such a mechanism to explain the persistance and unremitting course of some of the most stubborn human cases of pyelonephritis. One of the prime tools of those who study lupus and allied diseases has been the fluorescent labeled, anti-human gamma-globulin serum made in a rabbit. The fluorescent tag attached to this antiserum makes it possible to localize concentrations of gamma globulin in the lesions of lupus, periarteritis, thyroiditis and related disorders. Whether these concentrations of gamma globulin detected in the lesions by this tagging technic are the result or the cause of these diseases is now a matter of debate. At least it is clear that marked changes in serum proteins accompany these diseases. In the case of chronic pyelonephritis studied by this method there are no concentrations of gamma globulin in the renal lesions. It seems unlikely, therefore, that the progress of chronic pyelonephritis has the same pathogenic mechanism as that of the so-called collagen diseases.

The above general comments on bacterial pyelonephritis can be summarized by saying that there is an interplay of parasite and host factors in the development of renal parenchymal infection. In general, the bacteria are resident organisms of low virulence. They establish infections by ascending or hematogenous routes. By themselves even these invasions do not cause disease. In the presence of obstruction, either luminal or local within the kidney, infection is likely. The local defense mechanisms in the kidney are less well devel-

oped than in other organs. Biochemical factors in the kidney and defective host immune responses may also contribute to local infection. Whatever the mechanism by which infection starts, healing is slow and recurrence likely unless obstruction is relieved. Appreciation of these principles is essential to obtain satisfactory, long-term clinical results. Of greatest importance, treatment with antibacterial therapy should be adequate to kill bacteria. Furthermore, it should be continued until deep tissue infection is controlled and, finally, it should be accompanied by correction of contributing, predisposing mechanical factors.

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Question and Answer Session

Dr. Schreiner: We have some very stimulating and difficult questions. The first group deals with objections which have been raised to the use of a catheter. I shall read one question to show how the thinking goes: "In every discussion I have heard on pyelonephritis, instrumentation is always mentioned prominently as an etiologic factor. I do not believe, however, that there has been a reduction in the frequency of cystoscopy, retrograde pyelography or passage of sounds, especially in the female. Are these procedures themselves responsible for the high incidence of pyelonephritis or is the urologist able to avoid these complications?" Dr. Garvey, I think we should give you the right to defend the catheter first.

Dr. Garvey: I believe that the trend toward maligning instruments has got out of bounds and is being pushed by some who have forgotten the indications for, and the rational use of these instruments. Failure to use a catheter when it is needed can be serious and can produce greater complications than may occur with its appropriate and careful use. I also believe that the recent wave of enthusiasm for midstream samples of voided urine in the female can only be as good as the technic employed which at the best, in my opinion, in most institutions is not adequate for microscopic or cultural study of the urine. I believe that it varies somewhat with the person who does it. On the wards in our hospital as well as in a number of other hospitals where they ask for a voided specimen in the female, with a midstream catch that is done in bed by a student or a graduate nurse, maybe late at night and with the use of a light, it is just nonsense to expect to get an accurate culture or evaluation of the urine in those cases. On the other hand, I think that when catheterization is done in the urologist's office, where the staff is aware of the dangers of injudicious catheterization, when the genitalia are cleansed thoroughly and the catheterization is done by two people the danger of introducing infection is very small indeed. I believe further that most of the bacteria in the normal urethra which are introduced with a catheter are not pathogens, and that the patients who get flare-ups from instrumentation or infection already have a pathologic condition in the urethra with pathogens present. Unfortunately, in most institutions catheterization is done by but a small percentage of people from the Urology Department. Talbot, in a recent symposium, brought out that only 20% of catheterizations in their institution were done by members of the Urology Department.

Dr. Schreiner: I do not think there is any question that the catheter is an abused instrument. It is our repeated experience that still, after all that has been written and said, almost every anuric patient who is shipped to us for dialysis in our particular unit arrives with an indwelling catheter. This seems to be a "reflex" that people have,—namely, that they need to know exactly the first 100 cc. of urine secreted by an anuric patient and, therefore, this justifies an indwelling catheter. I can think of very little reason for catheterizing an anuric patient, and every single one of these patients develops secondary infections. Until beginning diuresis, the amount of urine passed by the anuric patient is relatively insignificant for metabolism and can be easily accounted for in fluid therapy. Second, when the patient begins to void he will usually let you know, and the most you need to do is intermittent catheterization under careful technic during the early

stages when he may be having difficulty in voiding. I can think of nothing more malignant than leaving a rubber tube in a dry bladder that is not being bathed by urine, and we have noticed some horrible infections as a result of this. I should like to ask Dr. Garvey one loaded question: If he really believes that most of these catheter-induced infections result from a stirring up of a pathologic condition already present, then how does he make the statement that improved technic is going to help things? If these are not organisms being introduced from the outside, is not the very act of catheterization itself the critical thing?

Dr. Garvey: I believe that most of the infections induced by the urologist are in males with chronic prostatitis or urethritis, or in children or in adult women with posterior urethritis. I am presuming that we are using a careful technic in the passage of catheters and instruments, which is a different matter from injudicious use of the catheter that is not sterilized properly, is too large, too rough and is not lubricated properly.

Dr. Schreiner: Is there any technic available for measuring ureteral reflux—vesicoureteral reflux, without bladder catheterization? Have you ever been able to do this at the tail end of, or at a particular point during intravenous pyelography, for example? Do you ever obtain stand-up micturition urograms without catheterization?

Dr. Garvey: We have on a few occasions where the bladder was left partially filled before the intravenous pyelogram was done, but this was never quite satisfactory because, in attempting to demonstrate reflux, you have to know the cystic pressure. Now we have found some reflux that occurred at as low a pressure as 10 cm.; others require 40 cm. pressure, but they will show reflux, so from a practical standpoint it cannot be demonstrated satisfactorily without a catheter.

Dr. Schreiner: Did everyone hear Dr. Smythe's point that one of the places where we come up against a brick wall in the use of a catheter is the measurement of residual urine? If the patient has good renal function, as Dr. Kass has pointed out, one can use the dilution of P.S.P. as a measure of residual urine. Unfortunately, most of our patients in whom we really want this information, do not have a good P.S.P. function; therefore, we are often faced with the need for catheterization. But I have seen this done needlessly the day after an intravenous pyelogram which offered an opportunity to see residual simply by having the patient void and then making another x-ray exposure in the same position to see how much dye is left in the bladder.

Dr. Garvey: One of the causes of infection which we see in postoperative urethrocystitis and which eventually may lead to pyelonephritis, is the fact that patients are allowed to go too long unable to void until the bladder has become over-distended and may develop a certain amount of paresis. Intermittent catheterization by waiting too long is very often a factor in this.

Dr. Schreiner: Would you agree that intermittent catheterization not waiting too long is preferable to indwelling catheterization?

Dr. Garvey: If it is done properly, I think it is probably better, provided one uses a small enough catheter, well lubricated. An inlying catheter for 48 hours with instillation of some antiseptic, I think is relatively safe.

Dr. Schreiner: I believe this is an important point. We have an institution in Washington called the Soldiers' Home, where there are a number of old boys walking around with catheters for years and years and tolerating them; but when these same people become bedridden for some reason or another they develop an overt infection. So I think the catheter in the ambulatory voiding patient on good water intake is a different instrument from the inlying catheter in the hospitalized patient lying quietly and who is dehydrated and putting out a low urine volume.

There are a number of questions here for Dr. Saphir. I shall try to condense them into a single one which has several points to it. Is it fair to exclude the urologic cases from your talks about hypertension inasmuch as many of Dr. Garvey's cases showed severe hypertension and Dr. Lange has seen it in children with urologic disease? Why do you wish to exclude this from your considerations of the relationship of pyelonephritis to hypertension? And second, how do you explain the patients who have pyelonephritis lenta and no hypertension?

Dr. Saphir: Any disease which is close to an artery and which is present for some time

does, perhaps as a reaction, cause intimal proliferation and fibrosis with consequent narrowing of the lumen. In the kidney it is this type of disease of the arteries which is responsible for hypertension and, as I stressed before, this arterial complication is very characteristic of the slowly developing pyelonephritis. On the other hand, there is no reason to assume that in certain cases of the destructive variety of pyelonephritis, which in a sense is also a chronic disease, occasionally changes in blood vessels as seen in pyelonephritis lenta may not occur. However, to produce hypertension in such cases enough functioning kidney tissue must be present. Hypertension does not occur if the main renal artery is completely occluded. In the destructive variety of pyelonephritis often so much kidney tissue is destroyed that in spite of the fact that there may be intrarenal arterial changes, hypertension does not ensue. However, I admit readily that there are instances of destructive pyelonephritis where there are also severe changes in the intrarenal blood vessels with consequent narrowing of the lumens and where there is enough functioning kidney tissue left so the patient may develop hypertension. But this is rare; at least much rarer than in the lenta variety. On the other hand, there are also a few cases of pyelonephritis lenta in which hypertension is not shown. As to the "why," the only answer is that for some reason a number of interlobar and arcuate arteries have been spared and the kidney is not an ischemic kidney. The reason why the blood vessels sometime may not be severely involved, may have something to do with the constitution of the patient, with genetics. But what I have discussed is true for a vast majority of cases,—in pyelonephritis lenta the blood vessels are involved and hypertension occurs. In severe destructive pyelonephritis hypertension may occur but is not common. A number of blood vessels may not show the type of arteritis deformans which is so very common in pyelonephritis lenta. Only in those cases where arteritis deformans occurs in kidneys with destructive pyelonephritis and where there is enough functioning kidney left, may hypertension occur.

Dr. Schreiner: An analogous situation to myocardial infarction obtains in renal disease and is shown by the relationship of hypertension to infarction. The patient who develops an inflammatory process which produces tissue ischemia and goes on to scar formation is better off, even though his pathologic lesions look worse, than presumably the patient who perfuses ischemic tissue. These are the patients in whom angiotonin is found in the renal vein or whose hypertension is improved if renal tissue is removed on that side, so it is not necessarily destruction but rather perfusion of ischemic tissue on which we must focus. We have heard a great deal about how the urologist is precipitating pyelonephritis, and maybe we ought to hear a little bit about how the internist precipitates pyelonephritis. Certainly two mechanisms have come to the fore recently—one is the development of hypokalemia, which is becoming an increasing problem with diuretic therapy, particularly with the newer tubular blocking agents; the other is the possible role of glucocorticoids in the immune mechanism. We shall ask Dr. Favour to comment on this point.

Dr. Favour: There are two mechanisms by which glucocorticoidal treatment may alter the course of a renal infection.

The first of these processes is metabolic. Glucocorticoids suppress leukocytic metabolism in geometric proportion to the steroid level. More than 100 micrograms per 100 ml. of its equivalent cortisone or glucocorticoid inhibits migration of cells into inflammatory sites, phagocytosis and bacterial digestion. Even in the presence of adequate antibacterial antibodies, this suppressive effect is present. As a result, bacteria which may have been ingested are not destroyed so rapidly and may be carried to other parts of the body. And if an infection already is in progress, bacteria can multiply locally more freely than they do under normal conditions. In the case of infections of the urinary tract this means that gram-negative bacteria can liberate their toxins in greater quantity. This in turn causes further tissue damage and extends the infection.

The second mechanism is an outgrowth of the first. Acute renal papillitis has occasionally been seen in patients on a high dosage of steroids. This phenomenon can be reproduced in animals also. Apparently the acute hemorrhagic necrosis of papillae is a Schwartzman-phenomenon type reaction. In the presence of excess steroids this occurs without the usual interval between first, the deposit of toxin in the tissue, and the later arrival of

toxin via the blood stream which sets off the explosive portion of the Schwartzman reaction.

Dr. Schreiner: Dr. Favour, do particular coliform strains, by repeated phage typing, cause pyelonephritis, getting back to the immune point again? Also, are recurrent attacks in the same patient caused by the same or by different strains?

Dr. Favour: A systematic study of this problem has not been done. We do know that the same spectrum of antibiotic resistance is seen in some recurrent infections suggesting that recurrence may be due to the same strain. There have been occasional studies indicating that a poor immune response follows a given infection. Perhaps for this reason the recurrent infection can be due to the same bacterial species.

Dr. Schreiner: We should agree that there are certain kinds of bacteria which, by their very nature, make for chronicity, for example, Proteus which now is believed to have an intracellular component. I should like to ask Dr. Lange and Dr. Smythe if they have also had the same experience that we have had. We have one patient whom we have been following on long-term treatment now for almost 9 years, and who had nothing but malaise and fatigue, with recurrent bouts of Proteus pyelonephritis. However, on two occasions she became acutely symptomatic with renal tenderness and fever, when the flora shifted to *E. coli*. Her Proteus pyelonephritis characteristically is a lenta type, and all she has is mild hypertension and recurrent fatigue and malaise. Has this been your experience, Dr. Smythe?

Dr. Smythe: I can't really answer that question. Some patients start off with perhaps an *E. coli* or an Aerobacter infection and then something will happen: intercurrent pregnancy, an operation or something of this sort, and they will develop a Proteus infection, and we will probably be unable to get rid of that Proteus once developed. It seems to me that the flora in these people shifts very rapidly and readily. At least the organisms that one recovers from the urine confirm this. I have also noticed that the organisms will shift especially in response to chemotherapeutic agents. I should imagine that what happens is the same sort of thing one sees with staphylococci,—you start a patient on treatment and let's say he has *E. coli* in the urine, sensitive to the drug that you are using. This organism will disappear and the urine will have low counts for a period of a few weeks, and all of a sudden a resistant organism, perhaps again an *E. coli,* will reappear in the urine.

Dr. Lange: We also have experienced the common occurrence of a shift of organisms in patients with chronic pyelonephritis. I should like to ask Dr. Smythe whether it is understood that all these urine cultures are taken after the patient is off any drug for at least 48 hours?

Dr. Smythe: No, the urine cultures I have illustrated here were taken while the patient was still on the drug. Para-aminobenzoic acid was added to urines of patients receiving sulfonamides.

Dr Schreiner: This, of course, brings out the point that Dr. Lange is making that, if you have a drug in the urine which preferentially inhibits growth on the plate of one organism versus another, even though you have a mixed infection you may apparently grow out the organism which is the least susceptible to that particular antibiotic. This is really urinary suppression or suppression of infection because, if you take the patient off a drug, you may come back to finding the original three organisms that were there all the time, whereas one might grow out on the plate, if it is done during the time when the patient actually has bacteriostatic levels of the drug in the urine.

Dr. Smythe: This is the reason why I have tried to stress so strongly that one should be suspicious of bacteriologic response when a patient is still on a drug. There is much more to this disease than just the disappearance of bacteria from the urine.

Dr. Lange: Should one not make it a rule, as you have suggested once before, that all reports of urine cultures in patients with pyelonephritis should be made after they are at least 24 to 48 or, maybe 72 hours off medication in order to have data for comparison?

Dr. Schreiner: I think this is a point, although another way of looking at it is that one should do two cultures because the information could be valuable. We have had, for example, a patient who shows on culture before treatment, *E. coli* and Proteus simultaneously with different sensitivities, and we

select a course of therapy based on a blending of the best sensitivities of the two organisms. If we do a culture 2 or 3 weeks subsequently and show that *E. coli* has disappeared but Proteus remains, it follows that we must emphasize those antibiotics which are directed more toward Proteus. Perhaps the ideal thing would be to do a culture during treatment to find out which organisms are escaping, and then to do another 4 to 7 days later to determine whether true bacteriologic reversal has taken place. Do you agree with that?

Dr. Favour: Yes, I agree. Dr. Smythe's discussion of the importance of long-term treatment and the emphasis we all have placed on the significance of clearing the urine completely, all suggest treatment must be for weeks and not days.

Dr. Schreiner: Dr. Kass and others have publicized so widely the cultural aspects of urine that the impression has been left in some people's mind that this was a disease of urine rather than a disease of tissue. Other people have taken the viewpoint that we need high systemic levels to get at the bacteria which are in the tissues, and they make the analogy of subacute bacterial endocarditis where bacteria can emerge from a fibrous area when not continuously "battered" by antibiotics over a long period of time. Other people have said that we should take both factors into consideration. I should like to take a quick poll of the panel on whether they think that too much or too little emphasis has been given to the bacteria in the urine versus bacteria in the tissues.

Dr. Smythe: It is easy to study urine and difficult to study tissue; therefore much emphasis has been placed on the urine because anybody can study it, and none of us has good methods for studying tissues.

Dr. Lange: I agree.

Dr. Saphir: I agree. An interesting investigation was carried out at the Boston City Hospital some time ago, and the conclusions were reached that it is not merely the presence of bacteria in the urine, but the fact that organisms rapidly multiply in the urine which can be demonstrated by repeated cultures, that is significant. It is not just that one may find organisms once or twice in the urine which is important. It should be demonstrated that they multiply rapidly.

Dr. Schreiner: There is an old paper that claims that urine by itself possesses normally an inhibitory factor to bacterial growth and that this is missing in patients with pyelonephritis. Do you think this might be true?

Dr. Lange: I should like to call your attention to another dilemma we are facing. It has been stressed that the acidity of the urine is one of the factors preventing the action of complement; on the other hand, there is a strong tendency to acidify urine in therapy. If you follow those lines of thinking, should one alkalinize urine to activate complement in the tissues?

Dr. Schreiner: That is a very good point. Dr. Epstein has shown that by simply taking a strain of animals and giving ammonium chloride and a standard strain of organisms, one can produce infection in a higher percentage of the animals that were acidified with ammonium chloride. Now this is in line with work showing that when you acidify urine you increase ammonia production and also glutaminase activity in the kidney. This may inhibit complement in the kidney. This is in direct conflict with the other statement that a low pH of the urine inhibits bacterial growth in the urine; thus, you must decide whether you want to acidify the urine to prevent bacterial multiplication at the expense of increasing ammonia production inhibiting complement at higher level.

Dr. Favour: We must remember that most of the gram-negative bacteria have a tough time growing in an acid environment, other than the typhoid organism. But then the question is, which is more important,—the urine or the tissue infection? If chronic pyelonephritis is due to re-infection contributed to by mechanical factors, what goes on in the urine may be very important. In this case the chief pathway for re-infection may literally be up the column of urine. This can be controlled with a simple program of therapy which would not be adequate for an infection of deep tissue.

Dr. Schreiner: I should like to point out that there is at least one situation where you can have your cake and eat it too, and that is in a patient who requires instrumentation for one reason or another. For this we have used a lactic acid drip directly into the bladder; if you do this you can acidify the urine without stimulating ammonia production—

an excellent way of keeping down bacterial counts without having to worry about the problem of sensitization of the patient to antibiotics.

Dr. Favour: Dr. Finnerty in our department has collected data on pregnant women with pyelonephritis albuminuria. His findings substantiated the figures which you heard Dr. Schreiner give from Dr. Kass' series. Dr. Finnerty also finds that 34% of pregnant women with albuminuria, who report for monthly observation, have asymptomatic bacteriuria. In other words, the finding of albuminuria more often indicates infection than it does a future toxemia of pregnancy. We now believe that all prepartum women should have one quantitative urine culture as part of their medical management.

Dr. Smythe: One does not prevent all pyelonephritis of pregnancy by placing these people on continuous chemotherapy. It looks very pretty on paper, but this is not the complete solution to the problem. I agree, however, with Dr. Favour that as a part of routine prenatal care, all patients should have a urine culture or at least a stain of urine sediment done in the second or third trimester.

Dr. Schreiner: For screening tests for people who are in practice, I advise one test which very few physicians do in their office, but which I still do routinely in mine,—an immediate stain of a fresh concentrated urine specimen taken in the morning.

Dr. Smythe: Centrifuged or uncentrifuged?

Dr. Schreiner: Centrifuged. If you do this, you have the same type of probability statistics as are involved in the sputum smears for acid-fast bacilli.

Dr. Favour: We should remember that we cannot see any bacteria in the stained, spun urine sediment unless there are more than 100,000 bacteria per ml. As a screening procedure, the methylene blue stain makes it easier to see bacteria than the Gram's stain.

Dr. Schreiner: Dr. Kass has pointed out that most of the women who develop terminal pyelonephritis had bacteriuria in the beginning of pregnancy, and this is fortunate because it gives one a long interval in which to treat the patient. We have been treating all of our pregnant women throughout the entire pregnancy, and we can carry most of them without any elevation of the blood pressure and without the succeeding difficulties.

In conclusion, let me summarize and say that we have discussed the problems of pyelonephritis that are presented by the obstructive disease, the problems of tissue resistance and tissue susceptibility to the host, the problems of what are the diagnostic criteria for establishing whether or not a patient has pyelonephritis, what are the criteria to determine whether or not a patient has been improved by therapy and how long he should be treated. As Dr. Smythe has pointed out, there are no dogmatic answers yet to the benefits of treatment. Our own particular routine is to treat with a bactericidal agent or combination of agents as the initial go-round for a two week period. Dr. Smythe treats for a one week period. No one can yet present scientifically adequate data to say that we have a rational basis for choosing one routine versus the other, for more statistics need to be gathered. I think the most important thing is that there is a positive obligation on the physician who sees the patient suspected of urinary tract infections not to say, "I am going to give you a drug for 3 days and you are going to be all right." What you should say is that you quite probably have a chronic disease that will require recurrent visits to the doctor, careful diagnostic procedures, long-term follow-up study, and probably intermittent courses of appropriate medication.

Dr. Favour: This is a shaggy dog offering from the poet laureate of the Renal Service. It was generated while sitting up here on the platform listening to all these august speakers:

There once was a bacterium named Proteus
Who deserted the colon most odious
To live in the kidneys more commodious.
He took off his boots in the tubular roots,
This buccaneer Luchia then feasted on urea,
Until it is now said, when the cultures are read,
That odious, malodorous Proteus bodes ill to us.

Dr. Schreiner: With that we will adjourn.

A Comparison of Cytologic and Histologic Findings in Patients Hospitalized for Pelvic Surgery*

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There is very good correlation between the histopathologic findings on tissue obtained at operation with that of cytologic smears made from material obtained by endometrial aspiration. In experienced hands the cytologic smear is thus a worthwhile diagnostic tool.

THE ABUNDANT CONFIRMATORY LITERATURE which has accumulated in the years following the original work of Papanicolaou and Traut[1] is adequate proof of the accepted place vaginal cytology has in the diagnosis of early cervical cancer. Unfortunately, vaginal cytology is not nearly as accurate when used as a screening method for endometrial carcinoma.[2-5] Although it has long been realized that endometrial aspiration can furnish adequate cells for study,[6] there has not been unanimity on its acceptability as a screening or diagnostic method. Schanze[7] found that in his hands its value was definitely limited, while Hecht,[2,8] Varangot,[9] Pundel,[10] and Iklé[5] believe the study of endometrial cells obtained by aspiration is of definite value in the diagnosis of endometrial carcinoma.

By comparing the cytologic and histologic findings in patients hospitalized for pelvic surgery, we hoped, (1) to determine the accuracy of the smears made by cervical scraping and endometrial aspiration, and (2) to clarify in our own thinking the place endometrial aspiration has in the gynecologic diagnostic armamentarium.

Materials and Methods

During the 6 month period of January 1, 1958, to July 1, 1958, cervical and endometrial cytologic specimens were obtained in the operating rooms of the George Washington University Hospital. Consecutive patients over 40 years of age hospitalized for gynecologic surgery were selected for this study. The cervical scrapings were secured with an Ayre spatula according to the method used in the George Washington University Hospital and its affiliated Cancer Clinic.[11] The endometrial aspirations were prepared by the technic described by Papanicolaou and Marchetti[6] and Cary,[12] using a 5 cc. control syringe with a 4½ inch malleable antrum tip.[11]

The cytologic specimens were processed in the cytology laboratory and interpreted and reported by one of us, and later reviewed by the other two.

Routine histologic interpretations of the cervical and endometrial tissues obtained at operation were made by members of the hospital pathology department. Copies of these reports were obtained for this study from the hospital record room to be tabulated and compared with the cytologic findings.

Results

There were 261 patients over age 40 included in this study. Table 1 shows the age distribution: 70.1% of the group were 40 to 49

TABLE 1

AGE DISTRIBUTION—261 CASES

Age	*No. Cases*	*Percentage*
40-49 yrs.	183	70.1
50-59 yrs.	53	20.3
60-69 yrs.	21	8.1
70-79 yrs.	3	1.5
80 plus years	1	

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years of age, 20.3% were 50 to 59 years of age, 8.1% were 60 to 69 years of age, and 1.5% were over 70 years of age.

The surgical procedures for which these patients were hospitalized were,—4 for biopsy, 34 for dilatation and curettage, 106 for dilatation and curettage and biopsy of cervix, 2 for trachelectomy, and 115 for hysterectomy.

Cervical cytology was available on 243 patients, or 93.1% of the 261 patients in the study. Surgical specimens were submitted for cervical histologic study on 252 patients, or 96.6% of the total. Table 2 summarizes the findings on cervical specimens.

Satisfactory endometrial cytologic samples were obtained on 174 patients, or 66.6% of the total. Unsatisfactory specimens were submitted on 71 (27.3%). No specimen was obtained on 16 (6.1%). Surgical specimens were submitted for endometrial histologic sections on 255 patients (97.7%). Table 3 summarizes the findings on the endometrial specimens.

As shown in table 4, there were 8 patients with cervical cancer, 5 of whom had intra-epithelial cancer and 3 invasive epidermoid carcinoma. Of the 5 intra-epithelial cancers, the cervical cytology was Class V in 4 patients and Class III in one. Endometrial cytology was unavailable in 3 of the 5 patients with *in situ* cervical cancer; it was of Class V on the fourth patient and Class I on the fifth. One of the 3 patients with invasive cervical carcinoma had Class V cervical cytology, while 2 had Class III. The one endometrial aspiration available on these 3 patients with invasive cervical cancer was reported as Class III on the basis of bizarre cells of squamous origin. The endometrial cells on this aspiration were normal.

There were 5 patients with invasive endometrial cancer. Four of the malignancies were adenocarcinoma and one was a mixed carcinosarcoma of the uterus. Of the 5 patients with cancer of the corpus, 4 had Class V endometrial cytology and one had a Class III report. The cervical cytology in these 5 patients was reported as Class III in 4 patients with unidentified bizarre cells and Class V in one, on the basis of malignant glandular cells (Fig. 5).

The photomicrograpns illustrate the comparable cellular findings on sections and smears. Figure 1 shows normal endometrial tissue and cells from a patient with carcinoma of the cervix.

Figure 2 shows material from a patient (not in Table 4) with endometrial polyps and Class II endometrial cytology.

TABLE 2

Cervical Cytology—261 Cases		
	No. Cases	*Percentage*
No specimen	18	6.9
Satisfactory specimens	243	93.1
Classification of Satisfactory Cervical Cytology		
	No. Cases	*Percentage*
Class I	7	2.9
Class II	206	84.8
Class III	24	9.9
Class IV or V	6	2.4
Cervical Histology—261 Cases		
	No. Cases	*Percentage*
No specimen	9	3.4
Specimens submitted	252	96.6
Histologic Diagnosis on Specimens Submitted		
	No. Cases	*Percentage*
No pathology demonstrated	11	4.4
Chronic cervicitis—183 Polyp— 20	203	80.6
Basal and endocervical hyperplasia— 4 Chronic cervicitis with erosion —16 Squamous metaplasia —10	30	11.8
Intra-epithelial cancer — 5 Invasive squamous cancer — 3	8	3.2

TABLE 3

Endometrial Cytology—261 Cases		
	No. Cases	*Percentage*
No specimen	16	6.1
Unsatisfactory	71	27.3
Satisfactory	174	66.6
Classification of Satisfactory Endometrial Cytology		
	No. Cases	*Percentage*
Class I	53	30.4
Class II	96	55.2
Class III	20	11.5
Class IV or V	5	2.9
Endometrial Histology—261 Cases		
	No. Cases	*Percentage*
No specimen	6	2.3
Specimens submitted	255	97.7
Classification of Specimens Submitted		
	No. Cases	*Percentage*
No pathologic lesion demonstrated—191 Pregnancy — 6	197	73.2 2.3 — 75.5
Polyp	33	12.6
Chronic cystic hyperplasia	26	10.0
Invasive adenocarcinoma — 4 Carcinosarcoma — 1	5	— 1.9

TABLE 4

PATIENTS WITH UTERINE CANCER

Patient	*Age*	*Para*	*Gravida*	*Endometrial Cytology*	*Cervical Cytology*	*Histology*
1. N.W.	40	o	o	*N.A.	V	Intra-epithelial cancer of cervix
2. M.U.	48	o	o	N.A.	V	" " " "
3. B.D.	62	i	i	N.A.	III	" " " "
4. N.G.	44	iv	iv	V	V	Cancer *in situ* in endometrium cervical polyp
5. M.G.	46	o	o	I	V	Intra-epithelial cancer of cervix
6. S.K.	60	ii	ii	N.A.	V	Epidermoid cancer with vascular invasion
7. M.B.	44	o	o	N.A.	III	Anaplastic squamous cancer
8. J.C.	68	N.A.	vii	III	III	Infiltrating epidermoid cancer of endometrium cervix —Stage I
9. M.S.	58	iii	iii	III	III	Adenocarcinoma of endometrium
10. G.L.	54	o	o	V	III	" " "
11. E.O.	67	iv	iv	V	V	" " "
12. A.P.	67	o	o	V	III	" " "
13. M.B.	69	o	o	V	III	Carcinosarcoma, uterus

*N.A.—Not available

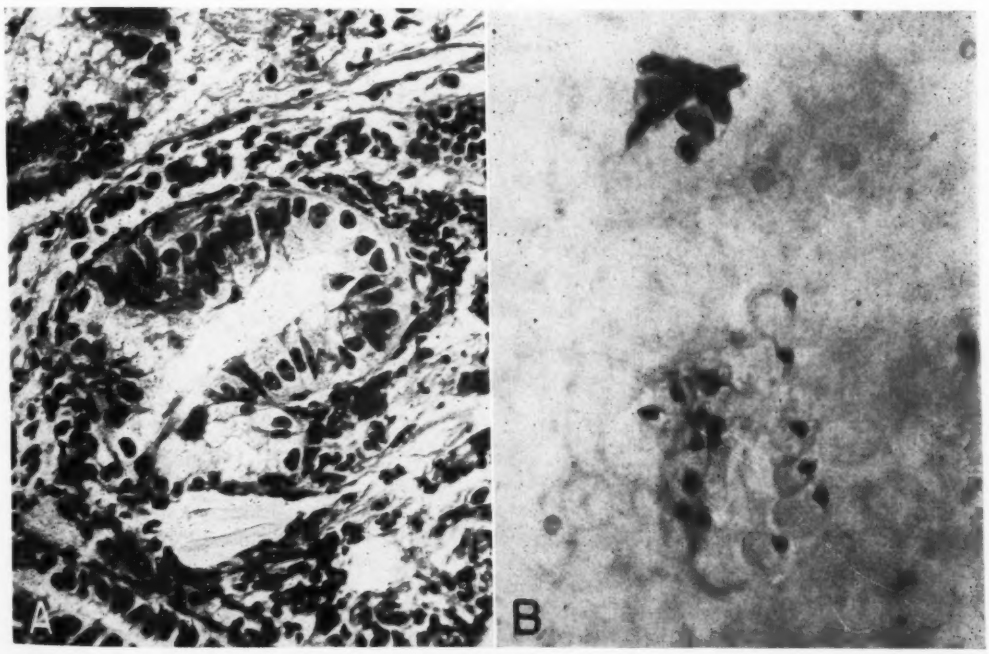
Figure 3 consists of sections from a patient, (not in Table 4) having squamous metaplasia and Class III cervical cytology.

Figure 4 demonstrates similar tissue and smear from a patient (not in Table 4) with cystic hyperplasia of the endometrium and Class III endometrial cytology.

Figure 5 shows tissue and smears from a patient (No. 11 on Table 4) with adenocarcinoma of the endometrium and Class V cytology on both endometrial aspiration and cervical scraping.

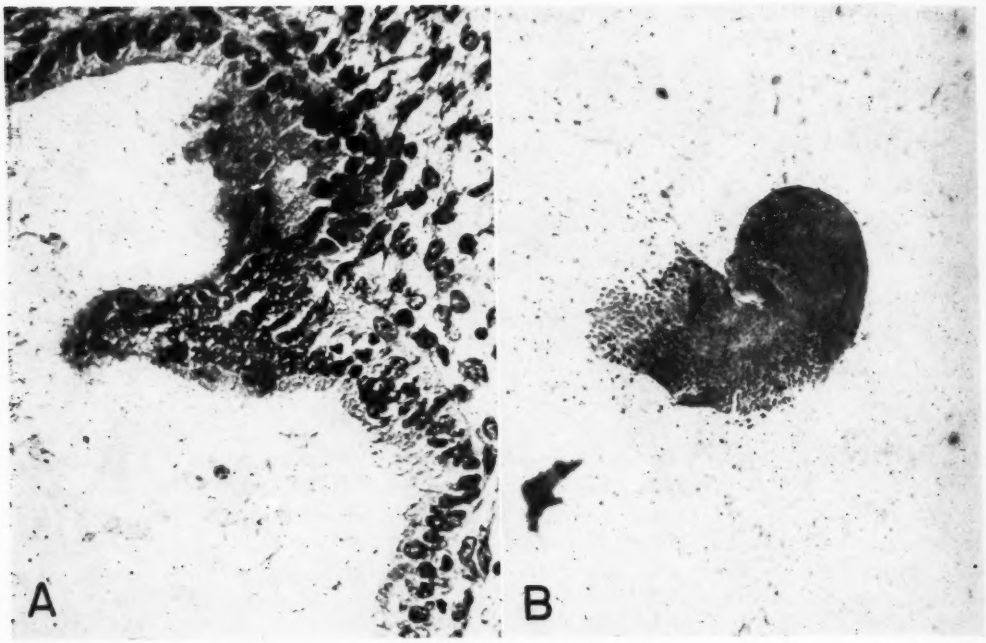
Figure 6 shows photomicrographs from a patient (No. 13 on Table 4) with carcinosarcoma of the uterus and Class III endometrial cytology.

FIG. 1



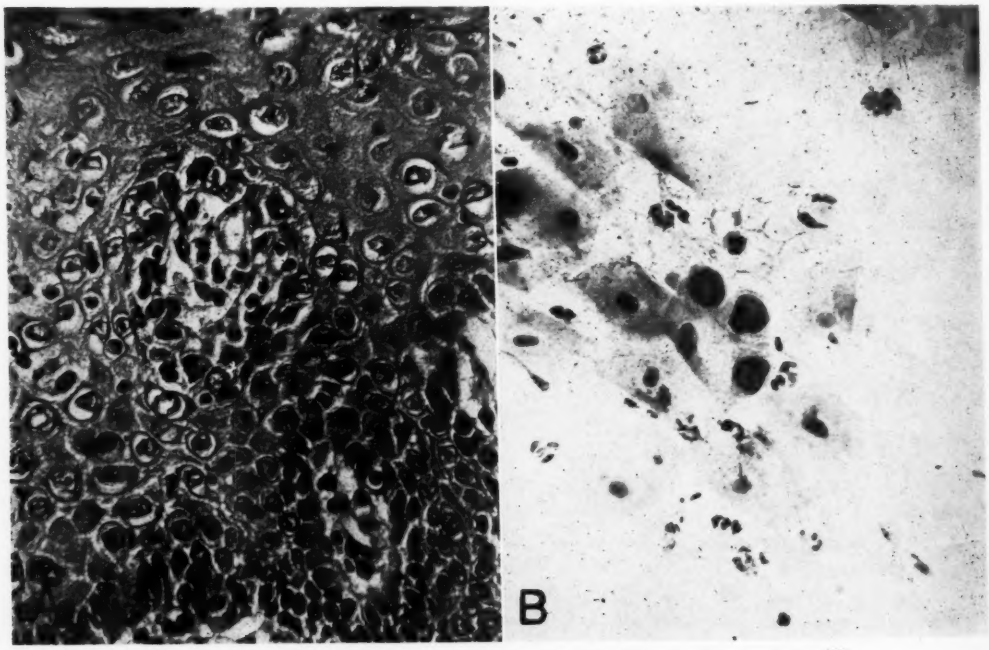
(Case 5, Table 4) Cervical cancer. (A) Normal secretory endometrium (x 430). (B) Smear from endometrial aspiration showing secretory endometrium (x 430).

FIG. 2



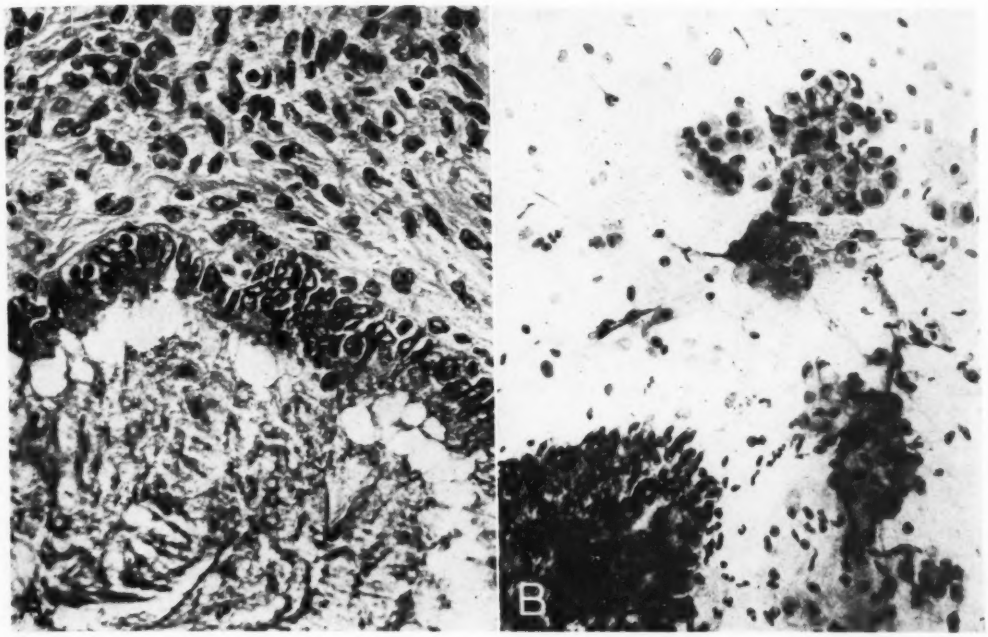
(A) Section of polyp (x 430). (B) Smear from endometrial aspiration; configuration suggestive of polypoid origin (x 100).

FIG. 3



(A) Squamous metaplasia of the cervix (x 430). (B) Class III smear from cervix (x 430).

FIG. 4

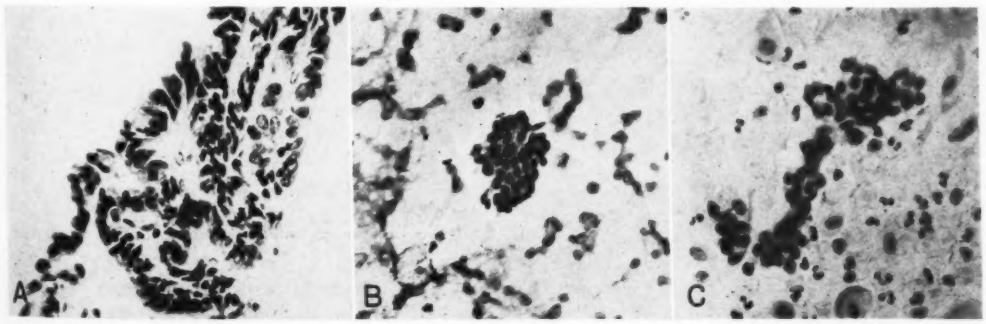


(A) Cellular atypism in endometrial hyperplasia (x 430). (B) Comparable atypism of endometrial cells on smear (x 430).

Discussion

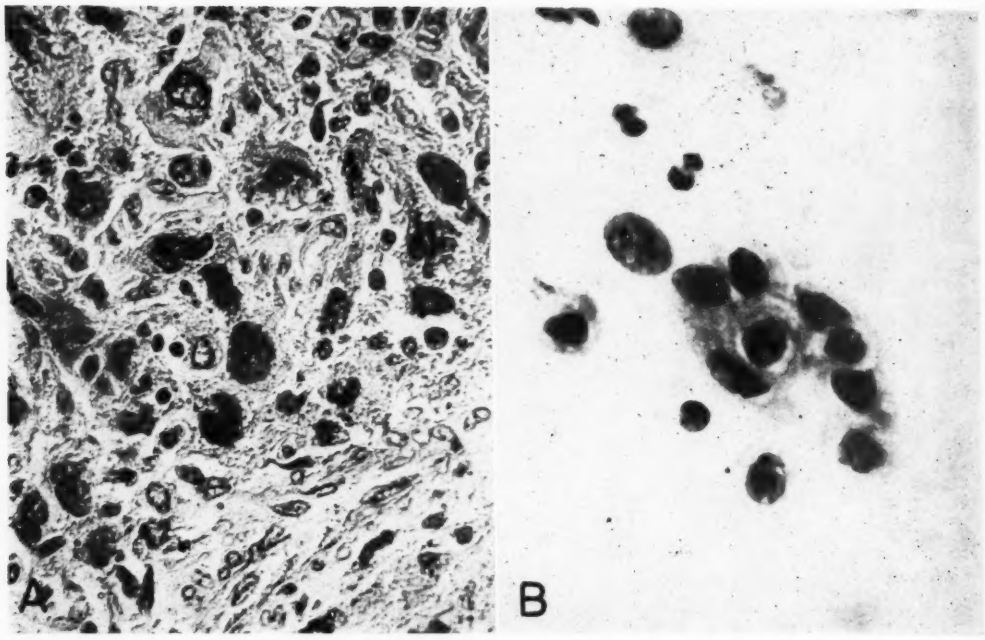
The 261 patients in this study represent a highly selected segment of the female population. No patient under 40 was included because of the general belief that endometrial cancer is seldom found before this age. Although the patients in this study were not selected on the basis of the presence of symptoms of pelvic disease, the fact that they were hospitalized for pelvic surgery indicates that they all had abnormal pelvic findings sufficient to require operation. It is interesting that in this group of symptomatic patients, 183 (70.1%) were between 40 and 50 years of age (Table 1). Five of the 8 patients with cancer of the cervix were in the fifth decade, while 3 were in their sixties (Table 4). None of the 5 patients with endometrial cancer were under 50 years of age, 2 were in their fifties, and 3 were between 60 and 70 years

FIG. 5



(A) Bizarre endometrial cells in small area (x 430). (B) "Positive" cells in smear from endometrial aspiration (x 430). (C) "Positive" cells on cervical smear (x 430).

FIG. 6



(A) Undifferentiated and bizarre cells in the section (x 430). (B) Similar cells in aspiration smear reported as "poorly preserved Class III," reclassified in retrospect as Class V (x 430).

of age (Table 4). The incidence of pelvic cancer in this selected group was 5% (13 cancers in 261 patients).

In tables 2 and 3, a relatively high degree of correlation can be noted between histologic and cytologic findings in regard to the distribution of percentage in specimens in most of the comparable categories. In these comparisons the comparable categories are shown in table 5. There seemed to be no histologic category comparable to the endometrial cytology of Class II, since most of the specimens with any finding less normal than chronic cystic hyperplasia were reported as "no pathology demonstrated." It is generally assumed that the greater the degree of histopathology found, the more bizarre the atypia of the exfoliated cells on the corresponding smears. That this is indeed the case is illustrated in the photomicrographs (Figs. 1 through 6).

The one Class V cervical smear obtained from a patient (No. 11 on Table 4) with adenocarcinoma of the endometrium shows malignant cells of glandular rather than epidermoid origin. If this patient had been investigated for cervical cancer only, the smear might have been considered as falsely positive (Fig. 5, A-C).

Comparison of tables 2 and 3 discloses a disproportionately high number of unsatisfactory endometrial aspirations submitted. Except in a few instances when the material was collected by the attending surgeon, the aspirations were done by residents and in-

TABLE 5

Cytology	*Cervical Histology*	*Endometrial Histology*
Class I	No lesion demonstrated	No lesion demonstrated Pregnancy
Class II	Chronic cervicitis, polyp	Polyp
Class III	Chronic cervicitis with erosion Basal and endocervical hyperplasia Squamous metaplasia	Chronic cystic hyperplasia
Class IV & V	Intra-epithelial cancer Invasive cancer	Invasive adenocarcinoma Carcinosarcoma

terns. As the study progressed a constant improvement in endometrial material for processing was noted. These observations would seem to indicate that Hecht[8] is correct in stating that endometrial aspiration is a procedure best left to qualified hands.

In table 4 we note that only one of the 3 patients with invasive cervical cancer had a Class V cervical smear. The cervical smears on the 2 remaining patients were reported as Class III. Often the superficial necrosis of an invasive cervical lesion will result in debris and poor detail in exfoliated cells making the cytologic evaluation uncertain. As is well pointed out by Graf,[13] this is one of the expected disappointments in the cytologic screening for cancer.

It is believed that aspiration smears, used by experienced physicians, can serve a highly useful purpose in locating the anatomic origin of malignant cells, be it exocervical, endocervical or endometrial. For example, the one Class I endometrial smear on a patient (No. 5 on Table 4) with *in situ* carcinoma of the exocervix illustrates a high degree of accuracy in obtaining the aspiration smear from the endometrium only. By contrast, one patient (No. 4 on Table 4) with intra-epithelial squamous carcinoma of an endocervical polyp had a positive aspiration smear. Since this patient did not have an endometrial lesion, one might possibly list this as a false positive endometrial aspiration. The smear is better listed as an example of poor technic in obtaining an endometrial aspiration, since the positive cells on the smear were obviously of the squamous series, and anatomically the early squamous carcinoma was found to be an endocervical lesion.

In no instance was there a report of less than Class III on a proven cancer (Table 4). If the opportunity had been present to repeat the Class III smears, it may be assumed that some of them would have been reclassified as Class V.

In this study no intra-epithelial endometrial lesions were found. All of the endometrial malignancies were invasive, symptomatic, and found in patients of an average age of 63 years. By contrast, among the cervical malignancies, 5 of 8 lesions were intra-epithelial, usually unsuspected from symptoms and found in patients of an average age of 48 years (Table 4). The accuracy of endometrial aspiration in this small series (4 Class V and 1 Class III from 5 patients with endometrial lesions) approaches 100% in these symptomatic patients. Hecht,[2] finding 85% accuracy, and Jordan,[4] with 84% accuracy, both advise routine use of endometrial aspiration as a preoperative precaution in patients who are candidates for hysterectomy. It might further be suggested from these observations that routine use of endometrial aspiration on all patients, at or beyond the menopause, regardless of symptoms or age, might possibly result in the discovery of early preinvasive endometrial cancers.

Conclusions

1. Endometrial and cervical smears and sections of tissue specimens obtained in the operating room at time of operation from 261 consecutive gynecologic patients were compared. This comparison showed a high degree of similarity of classification of the cytologic and histologic specimens from each patient.

2. Satisfactory endometrial aspirations are best obtained by physicians skilled in gynecologic procedures.

3. When obtained by experienced physicians, endometrial aspiration smears are accurate in locating the anatomic origin of malignant cells.

4. Routine use of endometrial aspiration on all patients at or beyond the menopause, regardless of symptomatology, might possibly result in the discovery of early preinvasive endometrial cancers.

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Discussion (Abstract)

Dr. James Henry Ferguson, Miami, Fla. The authors have done a service in pointing to the possibilities in the application as well as further development of better technics for cytologic studies in cancer of the endometrium. Although cytologic studies of the endometrium have not been as accurate as in other areas, notably in the cervix, the use of this diagnostic test is rewarding and with refinement we can expect greater accuracy in the future.

As has been noted Schanze, (Obst. & Gynec. 10:651, 1957), of my department, found that smears of material aspirated from the uterine cavity had limitations and substantially were no more accurate than cervical smears in screening for endometrial carcinoma. Furthermore, in 15 cases of endometrial hyperplasia atypical cells were noted in only three. In our aspiration of the uterine cavity for smears, we had to use a thin cannula in so many of the women that some of the tactile sense of the exact location of the cannula was lost. Frequently there was some doubt as to whether or not perforation of the uterus had occurred. The present unsatisfactory status of obtaining good smears is confirmed by the authors' observation that unsatisfactory specimens were submitted in 27% of their cases. We do not imply that the method had no future, since in the months of our trial with this technic we noticed some gains. For example, we improved our slides by the application of Hopman's new acetic acid technic for clearing the slide of blood (Obst. & Gynec. 11:267, 1958).[2] We have attempted to improve on aspiration of the uterus in an effort to make better smears for diagnosis. Although morphologic detail in the smears has never approached those made by scraping the surface of the cervix, we believe a comparable technic will be developed. Irrigations of the uterine cavity with saline and concentration of the sediment has not been encouraging. For a time we saw hope in irrigating the uterine cavity with trypsin or other enzyme preparations. The smears seemed better at times, but spillage of the solution into the peritoneal cavity caused a great deal of pain. We are working on a technic which we hope will prevent this discomfort during the examination.

In unpublished work done in my department recently, the records of all women proved to have endometrial carcinoma were studied, especially those in which a cervical smear had been made within a reasonable period of time. We found that 48% of these women had positive cervical smears. Though this does not approach the accuracy of cytologic studies in screening for cervical cancer, it is good enough to be considered a contribution to our diagnostic evaluation. Certainly positive smears from the cervix are leading us to a diagnosis of carcinoma of the endometrium at times. Unexplained positive cytologic reports are followed up by appropriate biopsies. When punch biopsy of the cervix has been negative, we plan a cone biopsy of the cervix, followed by curettage of any endocervical canal that remains and a curettage of the endometrial cavity. When this plan is pursued following a positive smear, it inevitably leads to an accurate diagnosis of endometrial carcinoma.

In the authors' report it seems that the aspiration of the uterine cavity was sucessful in the 5 patients who had invasive endometrial cancer. Four of the 5 women had Class V and one had a Class III findings. From our experience we are convinced that the Class III report deserves the same attention as a IV or V finding. As applied to endometrial cytology, all the aspiration smears made by the authors in the presence of endometrial cancer can be considered successful. Incidentally, the cervical cytology in these 5 patients with endometrial cancer would also be considered successful by us; 4 of the patients had a Class III smear, the other one having had a Class V. We emphasize that the Class III smear cannot be dismissed, but should be followed by diagnostic procedures which will inevitably lead to recognition of invasive endometrial cancer if it is present.

In the authors' table of the 13 patients having various types of cancer of the uterus (Table 4) we would consider, on the basis of our experience, that they had no false negatives. The 7 patients who had a cervical smear in the Class III category would be called positive by us. If these 7 Class III cervical smears were considered negative and the patient dismissed without further study, recognition of the diagnosis and treatment of these 7 patients would have been delayed.

In one of the case histories the authors quote a patient (No. 11 on Table 4) who had a Class V cervical smear and was eventually proved to have adenocarcinoma of the endometrium. They commented that if this patient had been investigated for only cervical cancer the true diagnosis would not have been revealed at once. We believe complete investigation of a positive smear, when there is no other explanation, should include a cone specimen and the curettage of the uterine cavity; if this had been done the case would not have been missed.

The conclusion of the authors is correct when they state that routine use of endometrial aspiration on all patients at or beyond menopause, regardless of the presence or absence of symptoms, will someday be valuable in the screening of early preinvasive endometrial cancer. The wider application of the technics and attitudes advocated by the authors should lead the way to this goal of an earlier diagnosis of endometrial cancer.

Carcinoma of the Breast*

GUY W. HORSLEY, M.D.,† *Richmond, Va.*

Here is a review of the present state of prognosis of cancer of the breast as related to treatment.

THE INCIDENCE of carcinoma of the female breast is still high. It has not decreased in the past few years, but the 5 year cure or survival rate has appreciably increased during this time. This latter, we think, is due to better worldwide education and earlier treatment of the condition. It is a well-known fact that if carcinoma of the breast is treated at Stage I when the lesion is entirely confined to the breast, the 5 year cure rate is quite high, but once the carcinoma has spread to the regional nodes, the cure rate is low. To my knowledge, there is no case on record in which a case of carcinoma of the breast which has extended to the distal nodes or other organs of the body, has ever been cured. Therefore, the problem of complete cure of carcinoma of the breast depends on early diagnosis and early treatment more than it does in other types of carcinoma.

The etiology of carcinoma of the breast is still unknown, and the frequency of this type of carcinoma varies a good deal with demography. It has been stated that the morbidity rate for carcinoma of the breast in rural areas is lower than in cities. In the United States uterine carcinoma is 60% more frequent in Negroes than in whites, while carcinoma of the breast and ovary is much more frequent among the white race. In Japan the death rate from carcinoma of the uterus equals that of the United States, but only one sixth as many women die from breast carcinoma. In India, the Hindu women who are poor, marry early, and have many children, have 50% of all carcinomas arising from the cervix, while in the upper classes, women who marry later in life and have fewer children, have 50% of all the primary carcinomas in the breast. In France, less carcinoma of the breast is found in women with large numbers of children than in those with smaller families. From these statistics, it can be easily seen that the incidence of carcinoma of the breast varies according to marriage, childbirth, hormones, heredity, and social status.

The majority of benign lesions, such as adenofibromas, intracanalicular adenosis, intraductal papillomas, and cystic disease, are all proliferated hyperplasia of the mammary tissue, and in all probability are produced by hormonal influence. Statistics have shown that there is a higher incidence of carcinoma of the breast in persons who have these pre-existing lesions than in those patients who have had no previous disease of the breast.

Nathanson[1] has stated that the effect of the hormones on breast cancer seriously challenges the theory on autonomy of cancer cells. Careful and continued observation of the effect of hormones on susceptible tumors should lead to an increased understanding of the mechanism of the growth process. The relationship of endocrines to certain types of carcinoma of the breast is well established. In 1932, Lacassagne[2] induced mammary carcinoma in male mice by injecting estrone benzoate, and it was apparent that an important step forward had been made in understanding the causes or the stimulating effect on mammary carcinoma. This led to a variety of interesting findings concerning the general effect of estrogen on neoplasm. Huggins and his co-workers[3] established in their experimental and clinical work on cancer of the prostate a very definite relationship between the male hormone and carcinoma of the prostate. It has been noted in experimental work that mammary tumors are more frequent in breeding than in nonbreeding mice, and in some strains the incidence of tumor is in proportion to the number of pregnancies undergone by the experimental animals. The incidence of tumors in these animals can be radically reduced by oophorectomy, and this incidence is also related to the age of the animal

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at the time of oophorectomy. These experiments have been substantiated time after time in the laboratory. Mammary carcinoma in the male mice of susceptible strains has been developed with all the natural and synthetic estrogen compounds that have been studied. The carcinogenic activity of these substances seems to be related to the amount of estrogen in the physiologic units rather than in the chemical structure or other properties of the substance injected. They can be administered subcutaneously, intramuscularly, or orally, with equal results, depending upon the physiologic activity of the particular hormone employed. The administration had to be continued for a prolonged period, 8 or more weeks, if the carcinoma was to develop at a later period. Compounds containing rapid elimination and consequently a shorter period of activity had to be given in larger doses and administered over a longer period than compounds given in subcutaneous implanted pellets.

In 1944, Nelson[4] was able to induce 68 carcinomas of the breast in 103 animals. He used the Long-Evans hooded strain. Fifteen years prior to this, there had been only four fibroadenomas noted in these laboratory animals. He gave daily injections of 50 gamma of diethylstilbestrol or subcutaneous implanted pellets of diethylstilbestrol. Metastasis developed in 33 rats. These were classified as duct carcinoma, adenocarcinoma, and duct and adenocarcinoma. Numerous other workers have repeated these experiments with essentially the same results.

Shimkins[5] stated that it is abundantly clear that in all species carcinoma of the mammary gland is the end result of an intricate and prolonged interaction and combination of at least several factors or complex of factors. In all species, a degree of genetic susceptibility and a degree of hormonal stimulation are essential. The process can be modified by numerous secondary influences of internal and external environment.

The cure for carcinoma of the breast is more discouraging in young women than it is in those women of postmenopausal period. Sittenfield[6] has stated that every cancer worker realizes that cancer of the breast in a woman under 40 years of age is a highly malignant disease. Notwithstanding the most thorough surgical excision and large doses of radiant energy, the end results are very grave and disappointing. Ewing[7] has also stated that in women under 30 years of age, carcinoma of the mammary gland is extremely fatal. Because of the disappointing results from treatment of carcinoma of the breast in young persons, in 1937, Dr. J. Shelton Horsley[8] adopted the procedure of removing both ovaries when a radical amputation of the breast was done for carcinoma of the breast in women in the premenopausal period. This procedure has been carried out continuously since that time at St. Elizabeth's Hospital in Richmond, Virginia. Several modifications have been made, but the essential principle of ablation of the ovarian function has been continued.

Surgical castration at the time of radical amputation of the breast for carcinoma was first suggested by Schinzinger,[9] but apparently he did not carry it out, although he discussed it before the Surgical Congress in Berlin on April 25, 1899. Doubtless, the procedure has been performed by other surgeons, although there seems to be no systematic record of cases previous to 1937. At first, we did bilateral oophorectomy on women under 40 years of age. This was then extended to all who were still menstrutating, and recently it has been extended to those who have menstrutated within the last 2 or 3 years. With the recent development of hormone assay, it seems logical to extend it further to include those persons who show by laboratory tests that their ovaries are still functioning and are producing estrogen, although they do not menstruate. It would seem, in these cases, that the stilbestrol stimulation tests might be of value in the postmenopausal patients when there is a question of whether oophorectomy should be done. It has been our experience that if ablation of the ovarian function is to be undertaken, a bilateral oophorectomy at the time of the radical amputation of the breast is the procedure of choice. It certainly does not prolong the operation. It can be done by either the surgeon or his assistant while the breast wound is being closed, and should not add to the risk of the operation.

It has been our experience that x-ray or radiation castration is not satisfactory. Among our early cases we had several patients who were given adequate doses of radiation therapy. They did not menstruate for several years, a few for as many as 5 or 6 years, and then at a later date menses returned. Under these cir-

cumstances, we think, to be absolutely sure that the ovarian function has been ablated, removal of the ovaries is essential.

In 1960 carcinoma of the female breast will account for approximately 24,000 deaths in the United States alone. It is the third most common of all carcinomas, and the most frequent one found in women, being more than twice as frequent as carcinoma of the cervix. Elman[10] states that although mammary carcinoma is one of the greatest cancer killers in the United States, many physicians are confused as to the best therapy, even with the earlier lesions. It has been shown that the 5 year survival is approximately 22% in the untreated cases and 59% for those treated, and the 7 year survival rate is only 9% for the untreated and 35% for those treated. Statistics from other clinics show there is an average survival rate of from 50% to 55% for 5 years, while there is a 75% 5 year survival rate in those patients who were in Stage I, and approximately 33% 5 year survival in those cases in which there were axillary or distant metastases.

The treatment of carcinoma of the breast has been carefully studied for the past century, both in this country and abroad. There are still some who doubt the wisdom of the radical mastectomy, and who have followed the advice of McWhirter,[11] doing a simple mastectomy to be followed by intensive x-ray therapy. A clinical evaluation of this material of McWhirter was done by Ackerman and others,[12] and it was shown that more morbidity and a higher persistence of the disease in the radiated field have been found than in similar cases treated by radical surgery. The opinion in this country seems to be overwhelmingly in favor of radical amputation of the breast when the malignancy is still in Stage I. The same procedure seems to be the treatment of choice in Stage II, in which the carcinoma has extended only to the regional lymph nodes without any palpable nodes in the supraclavicular areas, or in the opposite axilla, or x-ray evidence of spread outside of the breast. There is still much controversy over whether prophylactic oophorectomy or hormone therapy should be given in Stage I and Stage II. There seems to be a unanimity of opinion that oophorectomy should be carried out in Stage III and IV, and also in those cases in which the disease has recurred after the original operation.

In Stage I there should be no compromise with the use of minor surgery. The Halsted principle in the radical amputation of the breast should be carried out. This should include the removal of all of the skin over the breast, all of the breast tissue, the complete pectoral muscles from their insertion to their origin, the fascia of the serratus anterior muscle, the inner portion of the fascia of the latissimus dorsi, and a small segment of the fascia of the rectus abdominis muscle in the epigastrium. If the lesion is in the middle or inner portion of the breast, the dissection should be carried well across the middle to include some of the fascia over the origin of the opposite pectoral muscles. The axilla should be thoroughly cleansed, removing all of its structures except its major vessels and nerves, and care should be taken to clean out thoroughly the medial side of the axilla at the claviculosternal junction. Skin flaps should be cut thin, and I have found in my experience that less than 10% of these patients will need skin grafts if relaxation incisions are made and care is taken in the design of the original incision and in the closure of the flaps. Drainage under suction is most essential to prevent serum from collecting in the axilla, with subsequent edema of the arm, and to insure adherence of the flaps to the chest wall, consequently lessening the possibility of sloughing of these flaps. If enlarged nodes are found during the operation, they should be either tagged with black silk so the pathologist can readily identify them, and their position at the time of dissection should be noted, or they should be removed and labeled according to their position in the axilla. In this way the postoperative care can be more intelligently carried out if postoperative x-ray therapy is to be considered. I do not routinely do a biopsy on the parasternal nodes. In my opinion, if one node is found positive, experience has proved that the surgeon cannot be sure of the limits of the metastatic extension when one of these nodes is involved. If the lesion is in the middle or medial side of the breast, and microscopic examination shows there is extension into the lymphatics of the breast on this side, or if the lesion is close to the edge of the breast, it is advantageous to give deep x-ray therapy over the mediastinum and the internal mammary nodes. This will be much more efficacious than attempting a block dissection in this area or to pick out the nodes individually. If metasta-

ses are found in the axillary nodes, postoperative radiation therapy is administered to the points where metastases were found.

It has been our experience in cases of carcinoma of the breast in the premenopausal and menopausal person of 2 to 3 years, better results are obtained if surgical castration is done at the time of operation, and not to reserve this procedure for later metastases. Our statistics in 389 consecutive cases are somewhat similar to other published figures, there being 59% 5 year survival in all cases. This, however, is broken down into 57% 5 year survival in those without oophorectomy and 67% 5 year survival in those with oophorectomy, which is an improvement of 10 per cent. In the cases without axillary metastasis, the over-all 5 years survival is 80%, with 79% in those without oophorectomy and 87% in those with oophorectomy. In the cases with axillary metastasis, the over-all survival was only 36%, with 33% in those without oophorectomy and 45% with oophorectomy. Therefore, it can be seen in comparing cases in the same clinic, with the same surgeons doing the operations, there is approximately a 10% better survival rate in patients with oophorectomy than in those without oophorectomy. It is in the younger age group, in whom the 5 year survival had been much less than the average in previous years, that oophorectomy has been beneficial.

Recent advances in hormone therapy have added considerably to the prolongation of life. If used in early stages while the malignancy is still confined to the breast itself, and when used in conjunction with a radical mastectomy, 10% more cures will result. The ablation of endocrine function alone has never accounted for any known cure.

The care of the patient with recurrence of distant metastasis is still an unsolved problem. While no complete cures have been recorded, 5 and 10 year survivals after extensive metastasis have occurred. There is one case which I have frequently mentioned in which the operation of radical mastectomy for cancer of the breast, with ovarian ablation by x-ray, was done in 1940. This patient had her first local recurrence in 1946, which was treated by excision of a portion of the chest wall, followed by x-ray therapy. Her next recurrence was in 1952, being the same type of recurrence. In 1956 she developed obviously extensive bony metastasis. Two months before the metastases was noted, the patient, at the age of 50, began to menstruate again. X-ray examination showed extensive metastasis to her pelvic and leg bones. At that time she had a surgical oophorectomy and immediately improved. The leg brace, which had been used because of impending pathologic fracture, was removed. However, she had some recurrence of her pain in January 1956, and she was started on prednisone and testosterone. She was kept on this with occasional omissions until her death in 1959, 19 years after her original operation, 13 years after her first metastasis, and 3 years after her extensive metastasis to the bone.

If patients return with metastases, after a thorough evaluation as to whether the metastases are in the soft tissue, bones, lungs, or other structures, it is then decided what type of treatment should be given. Of course, if oophorectomy has not been done, or if there is any indication that there is active ovarian function, oophorectomy is carried out. If the lesions seem to be predominantly osseous, and the patient is under 65 or 70, she is usually started on doses of androgen, using 50 mg. of testosterone every day for the first month and continuing this on with approximately 100 mg. of testosterone twice a week for a total of three months. However, the patient has to be watched during this time as to signs of masculinization, and if these occur, the dose is either temporarily discontinued or drastically reduced. If, following this treatment, improvement does not seem to occur, we have obtained very good results from using prednisone, giving smaller doses than are often recommended, starting off with from 20 to 30 mg. a day for several days, and then reducing it, occasionally to as low as 5 mg. a day. This seems to make the patient feel more comfortable, has certainly given clinical evidence of reduction in the distant metastasis, and has promoted a feeling of well-being. The few cases in which we have done adrenalectomies and hypophysectomies do not seem to have survived any longer or have been any more comfortable than those who have been followed on the above regimen. At the present, we are using the cortisone and hormone therapy rather than adrenalectomy and hypophysectomy.

Much more research, both experimental and clinical, must be done to improve the present disheartening results we are obtaining in the treatment of carcinoma of the breast. In the

meantime, we must not compromise the treatment or the patient, but must use all our known resources and treat these patients early and vigorously. The public must be educated to seek early treatment and the doctors educated to use all of our present-day knowledge and skill. Until some better method is evolved, radical surgery, hormone ablation, and x-ray therapy should be, and is, the treatment of choice.

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The Intensive Care Unit and the Anesthesiologist*

PETER SAFAR, M.D., *Pittsburgh, Pa.*, ROBERT A. ABRAHAM, M.D., THOMAS J. DEKORNFELD, M.D., FREDERIC G. HUBBARD, and JOSEPH S. REDDING, M.D.,† *Baltimore, Md.*

The centralization of the acutely ill, who need special attention, in an Intensive Care Unit, makes for extraordinary care in certain situations of emergency. The authors point to the role of the anesthesiologist under such circumstances and the value of training residents in anesthesiology in such an area.

MOST HOSPITALS have acquired *postanesthetic* recovery rooms in which patients remain until they have recovered from the anesthesia. In some hospitals the function of this room has been expanded to that of a *postsurgical* recovery room, which is staffed around the clock to provide care for the surgical patients as long as they are critically ill. A further step has been the establishment of an Intensive Care Unit to which not only surgical but also medical patients are admitted, to provide continuous, specialized attention and treatment.[1] Patients of all services, when in the Intensive Care Unit, benefit from the concentration of skills and special equipment available there.

Three years ago the Department of Anesthesiology of the Baltimore City Hospitals in combination with the other clinical services and the nursing staff established a combined Intensive Care Unit-Recovery Room. Our residents in anesthesia and staff anesthesiologists, who are consultants in the treatment of all respiratory emergencies and of all comatose patients, have found that the Intensive Care Unit greatly facilitates their work because of concentration of patients and equipment in one area.

The purpose of this paper is to report some of our experiences with such a unit in the hope that some colleagues may be interested in the problems we have encountered.

*Read before the Section on Anesthesiology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

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(A) Progressive Patient Care

In the conventional hospital patients are grouped according to their diseases. Progressive patient care is the organization of hospital facilities according to the intensity of care which the patients require: (1) Intensive Care Unit; (2) Intermediate Care Unit or Acute Unit; (3) Chronic Care Unit; (4) Self-Care Unit; and (5) Home Care Program.[2]

Many hospitals have incorporated some of these elements into their organization and it is difficult to state where the concept of progressive patient care originated. The Manchester Memorial Hospital in Manchester, Connecticut, was one of the private hospitals which pioneered progressive patient care.[3] Among the larger teaching hospitals, the 2,000 bed municipal Baltimore City Hospitals has been operating a four phase program since 1936. All five phases of progressive patient care did not become effective at the Baltimore City Hospitals until the Intensive Care Unit was established in 1958.

(B) Economics

The average cost per patient per day at the Baltimore City Hospitals is shown in table 1. There is no doubt that a complete progressive patient care organization not only improves the care of the critically ill patient but also lowers over-all hospital operating costs. The establishment of an Intensive Care Unit in an existing conventional hospital results in initial expenditures for new equipment and for structural changes. Indeed, in a private hospital the high cost per patient day in the Intensive Care Unit will not lower over-all hospital costs, but this fact must be

TABLE 1

PROGRESSIVE PATIENT CARE AT THE BALTIMORE CITY HOSPITALS 1960

	Beds	Avg. Cost Per Patient/Day Approx.
Intensive Care Unit-Recovery Room	17-20	$50-80
Acute Unit	375	$27.00
Chronic Unit	431	$13.00
Tuberculosis Unit	337	$ 9.00
Infirmary and Self Care Unit	920	$ 4.00
Average total	2,083	$25.00 including physician's services

weighed against the added safety and more effective therapy to the critically ill patient. The Intensive Care Unit will lower the cost of hospitalization to the critically ill patient since the need for special duty nurses will be eliminated.

(C) Organization

The organization of an Intensive Care Unit must be planned according to local circumstances. Ideally, the postanesthetic recovery room should be separate and located on the operating floor, while the Intensive Care Unit should be located as nearby as possible. Due to limitations in funds, physical facilities and a severe shortage of nurses we had to combine the postanesthetic recovery room with the Intensive Care Unit.

Eight beds in our adult unit are set aside for postanesthetic recovery. This area is separated by a low partition from the area occupied by the patients who may remain in the unit for several days or weeks. Both areas are administrated as a single unit. Two side rooms provide 2 beds each for isolation and for the benefit of the patients who require quiet or darkened surroundings. Ideally the patients in the side room should be visible from the nurse's desk.

The necessary policies for the unit were established jointly by the chiefs of anesthesiology, medicine, surgery, obstetrics and gynecology, the director of the nursing service and the hospital director. We did not find it necessary to place the unit under the direction of a single department or physician.

The primary responsibility for any patient admitted to the Intensive Care Unit rests with the physician or surgeon admitting that patient. The anesthesiologist acts only as a consultant, although he may occasionally be requested to assume temporary management of the patient.

The chief of anesthesiology is responsible for, (1) coordinating the routines in the unit, (2) resuscitation, (3) respirator care, and (4) the teaching of resuscitation, tracheotomy care and other routines to the house staff and the nurses. One anesthesia resident is assigned exclusively to the Intensive Care Unit for one month. He maintains continuity of the special treatment.

We have a separate small Intensive Care Unit-Recovery area on the pediatric floor because of the special problems involved in the care of infants and small children. Except for this special situation the establishment of separate Intensive Care Units for each clinical service defeats its main purpose, namely the concentration of personnel and equipment.

(D) Admissions and Discharges

The patient is admitted to, and discharged from the unit by the chief resident of his respective service. Due to the limitations in bed space in the unit, the staff anesthesiologist has to assign priority to patients to be admitted on the basis of most critical needs. We found it most important to guard against the admission of nonsalvageable patients.

Discharges from the unit are usually done following a discussion between the staff anesthesiologist and the physician responsible for the patient.

(E) Nursing

The Intensive Care Unit is a separate nursing unit, and staffed by nurses who work permanently in the Unit. We erred by starting the unit before the nursing staff could be specially trained. Recently we corrected this by conducting a special course for all Intensive Care Unit nurses (Table 2). Each session consisted of a lecture followed by supervised practice on patients in the unit. The course proved very successful and several nurses not assigned to the Intensive Care Unit were included among the students to maintain a reserve of specially trained personnel.

At times of acute nursing shortage we have used special duty nurses from an outside registry. This proved entirely unsatisfactory as they were not familiar with the special technics and routines used in our unit.

(F) Equipment

Equipment in the Intensive Care Unit should be as simple as possible and the tech-

TABLE 2

COURSE FOR I.C.U. NURSES

	Instructor
1. Recognition and treatment of respiratory distress, determination of blood pressure, pulse, respiration, respiratory and circulatory resuscitation	Anesthesiologist
2. Oxygen therapy	Anesthesiologist
3. Tracheotomy	Anesthesiologist
4. Respirators	Anesthesiologist
5. Respirators	Anesthesiologist
6. Hypothermia	Anesthesiologist
7. Spinal anesthesia	Anesthesiologist
8. Postoperative pain	Anesthesiologist
9. Care of unconscious patient	Anesthesiologist
10. Maintenance of patient's chart	Surgeon
11. Shock and I.V. therapy	Surgeon
12. Determination of blood pressure, pulse, respiration	Surgeon
13. Patient after gastrointestinal surgery	Surgeon
14. Patient after chest surgery	Surgeon
15. Patient after cardiovascular surgery	Surgeon
16. Patient after orthopedic surgery	Surgeon
17. Patient after urologic surgery	Surgeon
18. Patient after neurosurgery	Surgeon
19. Fluid and electrolyte therapy	Surgeon and Internist
20. Tuberculosis, isolation	Internist
21. Physical therapy	Internist
22. Special problems in care of medical patients	Internist
23. Special problems in care of obstetric and gynecologic patients	Obstetrician-Gynecologist
24. Summary of technics and equipment	Anesthesiologist
25. Examination	Anesthesiologist

nics should be standardized so they will be well understood by all personnel involved. Most of the oxygen equipment of the hospital should be concentrated in the Intensive Care Unit to minimize the work of the oxygen therapist. Resuscitation equipment, respirators, oxygen equipment and nebulizers are maintained in proper condition by the oxygen therapist in cooperation with the Intensive Care Unit nursing staff. Loss and breakage of equipment seem reduced because only trained people handle the special equipment. Since the Intensive Care Unit is air conditioned we find little use for oxygen tents which hamper nursing care, make it more difficult to observe patients, and usually provide lower concentrations of oxygen than the face tent or tracheotomy mask.

The number and type of respirators needed in the Intensive Care Unit depends upon the conditions treated. We have at present 8 Moerch piston respirators for controlled respiration. This respirator is reliable for long continued artificial respiration and is simple to operate, as was demonstrated during the poliomyelitis epidemic in the fall of 1960 when over 25 patients (as many as 13 patients simultaneously) were ventilated with intermittent positive pressure respiration via cuffed tracheotomy tubes. Our experience in a situation like this poliomyelitis epidemic has shown that the standardized use of simple equipment is most important. We also have 3 respirators of the Bennett and Bird type to provide both assisted and controlled respiration. We have not seen any clinical use for tank respirators (iron lungs).

The beds used in the Intensive Care Unit and Recovery Room should have a low headboard so the patient's head can be approached from the vertex. The equipment and beds should be arranged so all patients are visible from the nurse's desk and from the areas where nurses prepare medications.

(G) Treatment

The conditions treated in the Intensive Care Unit-Recovery Room during 12 months of 1959/1960 are shown in table 3. Approximately 2,000 admissions to the unit in this period included over 200 nonoperative patients. There were 150 respirator cases, not including the 25 poliomyelitis cases mentioned above. Recently the percentage of medical patients admitted to the unit has been increasing. The indications for prolonged passive hyperventilation with intermittent

TABLE 3

PATIENTS ADMITTED TO I.C.U.-RECOVERY ROOM IN 1 YR.*

	No. Admitted	*No. Died*
Surgery/Gynecology-Obstetrics		
Postoperative without complications	1,515	0
Postoperative with complications	181	27
Head injuries	30	7
Severe burns	5	2
Severe chest injuries	2	1
Total	1,733	37
Medicine		
Pulmonary edema	40	18
Pneumonia	35	15
Coronary occlusion	28	10
Poisoning and coma	17	0
Cerebrovascular accidents	15	6
Convulsions	10	3
Septicemia	9	5
Obstructive emphysema	7	1
Respiratory paralysis (polio, etc.)	6	2
Others	38	4
Total	205	64

*March 59/60

positive pressure respirations have also been widened recently.

Prolonged respirator care via tracheotomy tube initially posed many problems, some of which were solved only after trial and error.

(H) The Role of the Anesthesiologist

Our general concept of the anesthesiologist's role in the treatment of patients in the Intensive Care Unit-Recovery Room area is to supplement the activities of the other specialists in patient care. By resuscitating the seriously ill patient and by maintaining adequate ventilation and circulation, the anesthesiologist often is able to provide the internist or surgeon with enough time for diagnosis and treatment of the underlying primary disease process. Our anesthesiology residents spend about 30% of their time in consultations and in resuscitations outside the operating rooms, primarily in the Intensive Care Unit. The unit has proved to be an ideal place for the training of anesthesia residents in these specialized para-anesthesiologic fields and also served admirably for the teaching of house officers of other services and medical students.

Conclusion

Our experience with Progressive Patient Care and the Intensive Care Unit has been rewarding. The anesthesiologist who has interest in, and time for more than providing anesthesia service in the operating room, may contribute in his role as coordinator and instructor in the Intensive Care Unit, and as consultant and investigator in medical and surgical emergencies throughout the hospital.

Acknowledgment

The authors thank Drs. F. C. Chinard, G. Mirick, M. M. Ravitch and R. W. Steenburg for their cooperation.

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Discussion (Abstract)

Dr. Seymour Brown, St. Louis, Mo. After hearing Dr. Safar and noting the type and results of intensive care administered to the patients in this concept, one must immediately express his admiration for the dedication of the personnel and the cooperation of all departments to attain this organization and to achieve these results. There can be no doubt of the benefits to be derived from the combined organized use of specialized medical knowledge in the care and treatment of the critically ill patients.

Most hospitals now have postanesthetic recovery rooms and a certain percentage have additional areas which may be termed postsurgical recovery, or areas for the group nursing of critically ill patients, with some additional isolated aspects of this program. However, I believe relatively few places have a set-up as complete as that outlined by Dr. Safar in the Baltimore City Hospitals.

This brings up several interesting practical points for discussion in relation to the establishment of such units in private hospitals. Apparently this is controversial primarily from the financial standpoint, as well as from the problems of utilization and organization of beds by the admitting office in private hospitals. It requires a reorientation of ideas in patient care with further emphasis on centralization of equipment and personnel, in the belief that greater efficiency can be obtained both in the direct treatment and observation of graded progress of patients.

Four major points for discussion are:

(A) Cost of specialized building space and articles of specialized equipment with associated maintenance costs of equipment and bed space.

(B) Availability and training of personnel.

(C) Changes in the organization of staff responsibilities and possible delicate personal ethical relationships between physicians and patient-physician relationships.

(D) Shifting of patients in private hospitals with attendant problems of clerical accounting and personnel movements.

The first aspect is to be decided by the determination of all groups involved in procuring financial ability either for modification of present existing facilities or for addition of new facilities with certain funds to maintain the set-up until it can function well. Many hospitals already have many specialized articles of treatment inefficiently used and distributed throughout the hospital. Effect on patient care cost must be evaluated.

The second aspect, as we all know, is the problem of a great shortage of good nursing personnel. However, greater efficiency of relatively fewer personnel with better care of patients may be a partial answer.

The third aspect is one so fraught with controversy and emotional reaction that I do not intend to do more than bring it to your attention for discussion. It certainly can be solved as shown in organizations of full-time personnel, but private hospital staffs bring in other aspects.

Last, but not least, I would like to mention some problems that were stated to me by officials of hospital administration when I discussed this possible arrangement for our new hospital now in construction. These consisted of: concern of the admitting office of frequent movement of patients into different areas, knowledge of locations of patients, changes of charges of rooms, increase of personnel to aid in the various movements, and reserve availability of beds in numerous compartmented areas for free flow of movement.

Again I wish to thank Dr. Safar for his excellent paper and presentation of an idea which is so fundamentally sound and progressive in the care of patients, that we must make every effort to solve any difficulties in providing similar units for the care of patients everywhere.

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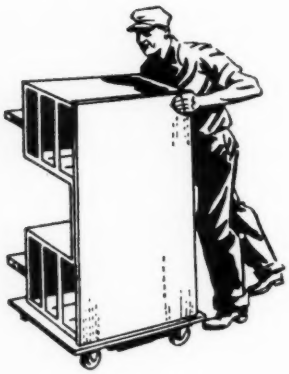

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Differential Diagnosis of Wheezing in Infancy*

LLOYD V. CRAWFORD, M. D.,† *Memphis, Tenn.*

Accurate diagnosis is essential to adequate and proper treatment in instances of "asthma" in infancy. Differential diagnosis is well considered in this paper.

THE DIFFERENTIAL DIAGNOSIS of wheezing in older children offers very few problems. On the other hand wheezing in infancy is often misdiagnosed.

The essential pathologic features of allergic bronchial asthma are spasm of the bronchiolar musculature, mucosal edema, and hypersecretion of thick tenacious material from the bronchial glands. All three of these basic pathologic changes occlude the lumen, are responsible for obstruction and result in generalized emphysema. Normally the bronchi dilate and elongate on inspiration and contract and shorten on expiration. Therefore the obstructive changes embarrass respiration more on expiration and are responsible for the expiration wheezing.

The younger the infant, the more chance the wheezing is due to other causes than hypersensitivity. The reasons for this are: (1) the relatively smaller diameter of the bronchial lumen; (2) the period of incubation necessary for production of hypersensitivity; and (3) the available evidence that suggests young infants are very poor antibody producers.

It has been shown that infants given antigen stimulation in the newborn period begin to form antibodies after a longer delay and to a lesser degree than infants injected with antigen at 6 months of age.[1] Another factor is that the gamma globulin fraction of serum, the fraction that contains most antibodies, usually falls from birth and reaches its lowest level in 2 to 3 months. Plasma cells, which are also closely associated with antibody formation, are present in the bone marrow in very small numbers at birth and only begin to make their appearance after 2 or 3 months of age.

Among the conditions to be differentiated from allergic asthma are infectious bronchitis, foreign bodies, vascular rings, bronchiolitis, mucovicidosis, congenital laryngeal stridor, pertussis, congenital lobar emphysema, and intrinsic and extrinsic pulmonary masses.

Diagnosis

The diagnosis of allergic asthma is a clinical one and depends on the composite of the history, physical examination, and laboratory findings. Any pathologic process leading to narrowing or constricting of the bronchial pathway may result in asthmatic-type of wheezing. This tendency is more marked in infancy than in the older child. A family history of allergic disease is often found in allergic asthma. The child who presents with allergic asthma frequently has a typical atopic eczema or a history of previous eczema associated with it. In most cases bronchial sensitivity has been preceded by nasal sensitivity. Therefore most asthmatic children will give a history of sneezing, nasal stuffiness, rhinorrhea and "allergic salute." If the patient is examined at the time of the attack there is usually obstructive emphysema throughout both lungs, dyspnea, and expiratory wheezing which is often dramatically relieved by epinephrine. The cytology of the mucous coughed up from the bronchial tract will reveal a predominance of eosinophils. Young children, however, have difficulty in coughing up this sputum. Because there is usually some degree of an associated allergic rhinitis, a study of the nasal cytology is a greater aid in making a diagnosis of allergic respiratory disease. The peripheral leukocyte count may show an increase of eosinophils. X-ray films of the chest in uncomplicated allergic asthma may reveal typical findings of generalized emphysema.

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In children the most common cause of wheezing to be differentiated from bronchial asthma is acute infectious bronchitis. Normally there is bronchial dilatation on inspiration and contraction during expiration. In young children this is more marked due to the greater elasticity of the tissue and lesser degree of calcification of the cartilagenous rings. In addition, because of the small lumen in infancy, bronchial edema without bronchial spasm is more apt to cause respiratory distress particularly on expiration. Acute infectious bronchitis usually responds poorly to epinephrine. Fever is present and there is usually an increase in white blood cells with no increase in the eosinophils. The nasal cytology is characterized by a predominance of neutrophils. Children with acute infectious bronchitis often have a negative family history of allergic disease. If the attacks recur at frequent intervals and become increasingly severe, the chances of the respiratory distress being caused by an allergic disease increases.

A foreign body in the bronchus may simulate an asthmatic attack. If there is any doubt, radiologic examination is mandatory. A metallic foreign body may be identified by a simple roentgenogram of the chest. On the other hand, a nonopaque foreign body may be somewhat more difficult to detect. Some objects, such as peanuts, contain irritative products that result in inflammation. Often fluoroscopic examination is more valuable than radiographs for the diagnosis of foreign bodies. If the history, physical examination, and x-ray studies leave any question as to the diagnosis of a foreign body, bronchoscopy should be done. A nonopaque foreign body causing a bypass valve-type of obstruction will not produce radiologic positive findings. On the other hand, in the check-valve type there is obstructive emphysema, which results in flattening of the diaphragm on the obstructed side and a shift of the heart and mediastinum to the opposite side. The difference is more marked on expiration than on inspiration. If complete obstruction develops, the heart and mediastinal structures are drawn toward the obstructed side and may remain there during both phases of respiration with the diaphragm on that side remaining high.

Occasionally foreign bodies in the esophagus may produce symptoms which are suggestive of allergic asthma. Although gastrointestinal symptoms, such as vomiting and dysphagia, are commonly associated, they oftentimes will be absent. The irritation of a foreign body often causes secretions that overflow into the respiratory tract resulting in considerable respiratory distress.

Congenital vascular rings may compress the trachea or bronchi and produce expiratory wheezing, which must be differentiated from bronchial asthma. The most common vascular anomaly is a double aortic arch. Other common anomalies are right aortic arch with left ligamentum arteriosum, anomalous right subclavian artery, anomalous innominate artery and an anomalous left carotid artery.

The symptomatology of vascular rings may be varied. The vascular ring often produces compression of the trachea and esophagus. The symptoms may be present in the early months of life. In addition to the wheezing respiration, the infant often tends to extend the neck and there is a brassy cough. Barium swallow and angiocardiograms may be necessary for diagnosis. The site of the tracheal obstruction is usually demonstrated on the tracheogram and after a barium swallow posterior indentation of the esophagus is often seen.

In infancy the syndrome of bronchiolitis may simulate an attack of asthma. This syndrome occurs most frequently in infants from 3 to 18 months of age. There is generalized emphysema with the thoracic cage being fixed in a position of extreme expiration with little excursion. The patients have very little fever. This syndrome does not ordinarily respond to epinephrine. Eosinophils are not present in the nasal secretion. However, at times, it is extremely difficult to differentiate an acute episode of bronchiolitis from an acute asthmatic attack in a young infant. If the bronchiolitis-like episode becomes recurrent, there is an increased likelihood of an allergic etiology. Wittig and co-workers,[2] in a recent follow-up study of 100 children with bronchiolitis, found that 49% developed respiratory allergy in later years. They suggest that there may be an etiologic relationship between bronchiolitis and asthma.

Fibrocystic disease of the pancreas produces a state of recurrent cough, wheezing and bronchial infection. In this disease, in addition to the general pulmonary disease, there is usually evidence of celiac syndrome. The expiratory wheezing may sound identical to bronchial asthma due to the thick tenacious secretions,

which are characteristic of cystic fibrosis of the pancreas. The determination of sweat electrolytes will reveal an increase of sodium chloride in patients with this disease. Usually the chloride content of sweat does not exceed 60 mEq./L. However, in cystic fibrosis of the pancreas the sweat electrolytes are usually greatly increased. A screening test has been developed where the patient's hand is placed upon agar saturated with silver nitrate. If the sweat chlorides are elevated, the hand print will cause a precipitation of silver chloride. Duodenal fluid may be obtained and tested for the presence of trypsin. Absence or a very low trypsin level in the duodenal fluid may aid in the diagnosis. In advanced cases, x-ray examination will show areas of generalized obstructive emphysema, patchy areas of atelectasis, areas of pneumonia, abscesses and increase in the bronchial hilar shadow.

Congenital laryngeal stridor is a frequent cause of dyspnea in children under a year of age. This is the most common syndrome that is mistaken for asthma in the first few months. In these children the obstruction is laryngeal rather than bronchial. There is often inspiratory stridor, hoarseness and brassy cough. There may be some retraction during inspiration.

On occasion pertussis may be confused with asthma. On the other hand, a severe intractable allergic cough occurring for several months in the spring may be responsible for the mistaken diagnosis of whooping cough. The history of exposure to other cases of pertussis may suggest the diagnosis of whooping cough. Leukocyte counts are not dependable but an increase in the total count as well as a high percentage of lymphocytes are suggestive.

Congenital lobar emphysema may be confused with the respiratory distress of allergic asthma. In these infants some local process, such as a kinking of the bronchus and the like, is responsible for a ball-valve mechanism and the production of a local emphysema. The x-ray film will show a large area of localized radiotranslucence with a shift of the heart away from the affected area. At times the treatment of children with congenital lobar emphysema is surgical.

Many types of masses in the chest may cause obstruction by pressure on the bronchial walls. The most common causes of extrinsic obstruction are lymph nodes, tuberculous nodes and Hodgkin's disease. Tuberculous granulations may cause an intrinsic obstruction. Usually when the extrabronchial lesions are large enough to be responsible for bronchial obstruction, they can be detected by x-ray examination. In tuberculous infection of lymph nodes, the tuberculin test is usually positive and generally there is an associated parenchymatous lung lesion.

Summary

The differential diagnosis of allergic asthma in infancy offers considerable more problems than in older children. The most common conditions to be differentiated are infectious bronchitis, foreign bodies, vascular rings, bronchiolitis, mucovicidosis, congenital laryngeal stridor, pertussis, congenital lobar emphysema and extrinsic and intrinsic pulmonary masses. For proper management of a wheezing infant, a correct etiologic diagnosis is necessary.

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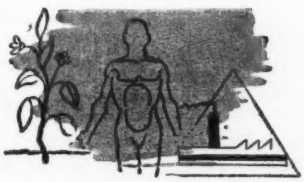

Selective Prefrontal Leukotomy in the Management of the Geriatric Patient with Mental Illness*

EDMUND A. SMOLIK, M.D., and FRANCIS P. NASH, M.D.,† *St. Louis, Mo.*

Age does not disbar an elderly patient from the advantages of prefrontal lobotomy if the indications are clear-cut.

THE PROBLEM of the management of increased numbers of patients suffering from psychiatric disorders in the advanced age group (geriatrics) is an expanding one. The recent deluge of pharmacologic agents which have had, in many instances, a beneficial effect upon mental and emotional disease, has in large measure decreased the indication for surgical management.

However, no matter how beneficial the results, no therapeutic agent or combination of agents are an absolute panacea.

In this age group particularly there may be contraindications to drug therapy, or there may be failure from such therapeutic regimens as electroshock therapy, insulin shock and the like. These latter may not be well tolerated because of other associated organic disease, such as cardiovascular disease. It is in such problem cases that selective prefrontal leukotomy may offer the patients the possibility of mental rehabilitation.

In an effort to determine whether, in fact, selective prefrontal leukotomy did offer such advanced aged patients a reasonable promise of result, we undertook to analyze the results in a group of patients whose age varied from 50 to 77 years upon whom we operated during the 5 year period from 1949 to 1954.

In all there were 87 patients. Of these, 69 were women and 18 were men.

All of this group were inpatients at St. Vincent's Hospital of St. Louis, under the care of the following psychiatrists: Dr. W. B. Lytton, Dr. P. Kubitscheck, Dr. S. Benet, Dr. E. Parsons, Dr. P. Hartman, Dr. R. Brooks, Dr. L. Hofstatter and the late Dr. R. Britt.

The psychiatric diagnoses were established at staff conference for the clinic group of patients or by psychiatric consultation for the private service. Recommendations as to therapy were established by these two methods.

Although these patients were hospitalized within a private institution, nonetheless, approximately 60% were cared for on the free clinic service.

The criterion utilized for determining the eligibility of a patient for operation was the chronicity of the illness. This was either the resultant of the lack of response to the then known medical therapies or the unsustained response to these therapies. Surgery offered the patients their last therapeutic resort as all other generally accepted treatments, such as psychotherapy, electric shock, insulin shock, etc., had been exhausted without beneficial response.

The following is the psychiatric classifications of this series of patients:

Involutional psychosis	33
Schizophrenia	27
Manic depressive	14
Senile psychosis	4
Psychosis due to circulatory change	3
Anxiety reactions	2
Psychosis with mental deficiency	2
Psychosis due to epilepsy	1
Psychoneurosis	1
Total	87

In 81 of these 87 cases a detailed history of previous psychiatric treatment was available. The duration of psychiatric treatment prior to operation ranged from one month to 64 years. The total treatment, both on an outpatient

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and an inpatient basis, given these 81 patients totaled 1,045 years and 6 months. The average was 12 years and 10 months per patient.

In 83 of the 87 patients it was possible to determine the duration of hospitalization. Each patient had multiple admissions and discharges often from various institutions. The duration of institutional care in this group of patients ranged from one month to 45 years. The total hospitalization of these 83 patients was 601 years and 7 months. This averaged approximately 7 years and 3 months per patient.

The treatment given these patients included the use of electric shock in 50 patients, insulin shock in 3 patients, a combination of electric and insulin therapy in 23 and Metrazol shock in 1 patient. Usually there was a history of multiple shock treatments in a given patient's history.

In 10 patients shock therapy was precluded because of associated organic disease, such as, emphysema, arteriosclerosis, heart disease, diabetes and/or hypertension.

Surgical Technic

In 1944, together with Drs. L. Hofstatter and A. Busch, we described the technic of limiting sections to the orbital quadrant. In a large series of patients this had proved an efficacious technic. Shortly after 1948, we modified our technic utilizing essentially the Lyerly approach and limiting the cut to the orbital median quadrant. All procedures are usually carried out under combined local and pentothal sodium anesthesia.

Results

Fifty-four of the 87 patients were discharged from the hospital following prefrontal leukotomy. The criteria for discharge in these patients was the absence of or the minimal residual of the mental aberrations which had been evident prior to operation. This was evaluated by the attending psychiatric staff. These patients following discharge from the hospital were maintained on what was termed a "trial period." During this period the patients were seen at frequent intervals by the psychiatrist. When, after a trial period which varied from 6 months to 2 years, the psychiatrist and family judged the patient to have made a normal social adjustment and in some instances to be gainfully employed, he was classified as "recovered" and permanently discharged.

In addition to the patients discharged, 12 of the 33 remaining in the hospital showed such improvement as to allow their advancement in patient classification, which allowed the patient greater hospital privileges. This permitted the release of nursing care.

In all, 60 of the 87 patients (68.9%) undergoing prefrontal leukotomy were benefited by the operation.

In the past five years, 6 patients who had been discharged have required rehospitalization. Thus, 55.1% of the patients operated upon have remained discharged.

Discussion

The entire series of patients has been followed from 5 to 11 years from the date of operation.

Of the 54 patients discharged, only 6 have required subsequent hospitalization, that is to say, they have "slipped." Of these, 5 had returned within a 2 year period and one returned after a discharge of 8 years. It would appear that if a patient had had a favorable result which lasted at least 2 years, the chance for permanent maintenance of the operative success appeared to be established.

Purely from an economic aspect it would appear that this procedure had, in fact, effected an extraordinary economic saving. On the basis of current rates of $15.00 a day the hospital cost of these patients prior to operation was $3,204,307.50.

In this series there were no deaths, no neurologic organic deficits such as hemiparesis and no infections. Since the patients were routinely put on anticonvulsive therapy consisting usually of a combination of phenobarbital and/or diphenylhydantoin (Dilantin), we have no statistical data on the incidence of convulsive seizures. From other cases of operation by a similar technic the incidence was in those groups less than 4 per cent.

From our experience in this series, the procedure as carried out produced results which were most satisfactory to the psychiatrist in the management of his patient, to the hospital economically which had maintained a great number of these patients and certainly to the family immediately concerned. In patients who were not able to leave the hospital, the

results in a substantial number enabled the liberation of these patients from custodial care thus releasing hospital personnel for other duties.

Many of these patients had had shock therapy and other psychiatric therapy which could not effect a resolution of the psychiatric problem. In another group, such therapy was precluded by the existence of coronary artery disease or other stigmas of cardiovascular disease.

Thus, under controlled anesthesia, a swift gentle operation obviates the hazards of shock therapy. We have established the fact that these patients do tolerate the procedure well with a minimum of hazard both in terms of mortality and morbidity.

Since this period, that is 1949 to 1954, pharmacologic and neurochemical strides have been made. Conceivably the surgical approach to these problems may be obviated. However, no approach generally is 100% successful in its therapeutic results. Hence, should such therapeutic measures be found inadequate, selective prefrontal leukotomy, as described here, offers a definite statistical hope for recovery from psychiatric ailment in the advanced age group which is increasingly becoming a problem.

SMA's 1961 Meeting

Dallas, Texas

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Manipulation of the Neuromuscular Unit Via the Periphery of the Central Nervous System*

MANFRED R. M. BLASHY, M.D.,† *Temple, Tex.*

The author deals with a relatively new concept in stimulation of muscle function through the exteroceptors of the skin surface. This would represent a stimulation of muscle groups by stimuli from its own skin area. This concept is contrary to certain tenets held in physiology.

MANY ATTEMPTS have been and are being made in the rehabilitation of muscle function to influence the neuromuscular unit by stimuli applied to the periphery of the central nervous system. Be it noted that the term "neuromuscular unit" (NMU) should include the majority of the components of the reflex arc, i.e., the exteroceptors with their sensory pathways to the spinal cord, the motor neurons leading back to muscle as well as the proprioceptors of muscle, predominantly the muscle spindles along with their own sensory afferents to the cord. Reasons for this will become clear later.

The use, for example, of primitive motor patterns based on the tonic neck reflex (Magnus, 1920) represents one of those attempts, the mass movement patterns utilized by Kabat and his co-workers[1-3] is another. These reflexes were considered so basic that a reintegration with what Fischer[4] has more recently called "higher levels of transaction" became feasible, indeed could be improved and accomplished.

This paper deals with restoration of muscle function by stimulation of the NMU, primarily the exteroceptors of the skin surface. The method is called *Orthokinetics.* It was originally developed by a German orthopedist, Julius Fuchs, who practiced in New York City in his later years and died in 1953. He used tubular devices made of leather in the treatment of fractures and other orthopedic disabilities combining support and mobility in an ingenious manner.[5,6] Since his approach and theory differ markedly from ours, we have retained only the name of the method and Fuchs' basic treatment unit, the so-called *orthokinetic segment.* This is a band-like cuff consisting of a combination of elastic with inelastic elements. It is applied to a dyskinetic extremity in a manner similar to the cuff of a blood pressure instrument.

Working with orthokinetic segments, we[7] discovered in 1954 that the elastic part of it becomes kinetically a facilitating field of muscle action, whereas the inelastic part becomes a kinetically impeding field when applied over antagonistic muscle groups of an extremity. This transformation of an elastic-inelastic orthokinetic segment into a neurokinetic device of surprising consequence is the first fundamental principle of orthokinetics. The orthokinetic segment, therefore, is by no means just a simple "bandage" but a neurokinetic tool which enables us to manipulate the NMU for the purpose of correcting or "righting" dyskinesias; hence the name orthokinetics.[7,8]

Figure 1 shows an orthokinetic segment drawn to scale. The interrupted lines are the cross-stitch pattern of the inelastic part. The strips on either end represent eyes on the left side, hooks on the right used for closing the segment. It is a thigh segment as suggested by the measurements of 7 inches for the elastic part, 10.25 inches for the inelastic. The diagonal direction of the eye-strip on the left compensates for the cone-shape of the thigh achieving thus a snug fit. The material is a rubber-reinforced elastic bandage, 4 or 6 inches in width; the segment is made in a continuous fold-over process until 3 to 4 layers

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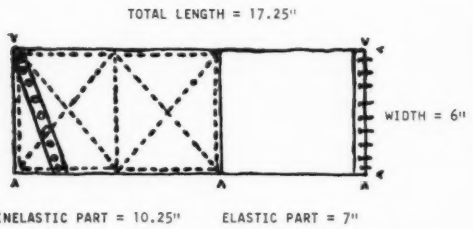
FIG. 1



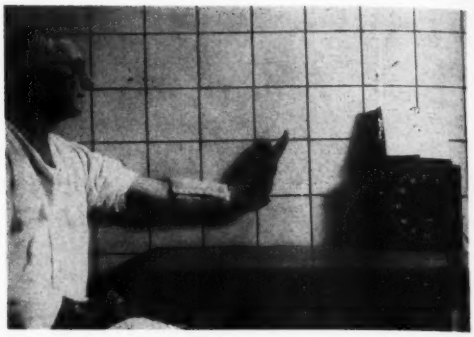
Orthokinetic segment for quadriceps facilitation drawn to scale: 0.25" = 1". Elastic part = facilitating orthokinetic field, inelastic part = impeding orthokinetic field. For other explanations see text.

are done. The material is made inelastic by inserting a measured piece of heavy canvas between the elastic layers and sewing them together in the cross pattern shown. Details of measurement taking and fabrication have been described elsewhere.[8] I only wish to stress here that the segments have to be made according to individual measurements of each patient.

Case 1. The segment in figure 1 was fabricated for a 26 year old white construction worker, who had a residual weakness of his right quadriceps group after poliomyelitis in 1952. Atrophy was marked: the normal left thigh showed 19 inches, almost 2 inches more than the value for the right. The power test produced only 7 repetitions with a 5 lb. weight, the 8th was already too weak to reach full knee extension. Immediately after the orthokinetic segment was made and in place, the patient was able to perform 16 repetitions with the same weight and had power to spare; but I was satisfied with a 100% increase in power on first trial. This took place on July 6, 1960.

On July 12, the patient performed 48 repetitions with the same weight. He had had 7 exercise periods (slow rotary type on a standing bicycle of 20 minutes duration) wearing the segment for 6 days for about 14 hours a day. As to the load increase,—he performed on the same day 25 repetitions: with 5 lbs. during the first 10, with 7 lbs. during the second, with 10 and 12 lbs. during the last five. The quadriceps weakness of 8 years duration was practically eliminated within 6 days.

FIG. 3



Case 2. The figures which follow are a photographic series of a 54 year old cattle farmer with weakness of extensors of the left wrist of several years standing. In recent months tools or dishes had fallen out of the left hand. He showed marked loss of power in his hand grip, pain in left forearm and slight numbness in the radial aspect of the hand. (Brachial plexus syndrome due to cervical arthritis with degenerative changes at C-5, 6 and 7 on x-ray examination.) The range of extension of the wrist is as follows:

Figure 2. Before orthokinetics=32° (with great effort; segment is on the table).

Figure 3. With segment in place, the elastic part covering the extensor group=facilitation of wrist dorsiflexion; the inelastic part=impeding orthokinetic field over flexor group. (The cross-stitch pattern reveals the inelastic part of the segments, one for the forearm, the other for the wrist) producing 64°.

Figure 4. The segments are reversed=23°.

The time interval between figures 2 and 3=46 seconds; between figures 3 and 4=52 seconds. Date: Oct. 28, 1959.

It is thought these pictures show true kinetic properties of the orthokinetic segments and are self-explanatory as such. After 9 days of orthokinetic exercises (rotary), 20 minutes

FIG. 2

FIG. 4

twice daily, the patient was discharged from the hospital free of pain and other symptoms. His dyskinesia, present for several years, had been restored to normal within 9 days.

These cases represent newly recorded evidence of what orthokinetic therapy can accomplish, and with an immediacy and totality never before experienced with any other exercise regimen or apparatus—at least to my knowledge—in physical medicine.

The types of disabilities treated so far comprise mainly three major categories: neurologic, with or without involvement of the central nervous system; degenerative arthritis; and a "post-orthopedic" group with dyskinesia due to disuse atrophy, pain, or dysfunction of joint, postoperative or otherwise, with corresponding changes in the kinetic chain as, for example, after joint fusion. The number of patients treated is at present one hundred and fifty. A positive response to orthokinetics has been observed in 79.5%, a negative one in 11 per cent. Another 9.5% have had questionable results for various reasons, such as lack of follow-up, or too brief an observation period. Since it is the purpose of this paper to discuss some aspects of the mechanisms involved in producing orthokinetic effects, a resumé is being presented here with special emphasis on those pertinent to the discussion to follow.

Resumé of Orthokinetic Effects

(A) *General Kinetics.*

(1) The kinetic properties of the orthokinetic segments—some of them shown in the photographs above—depend upon their composition, i.e., the combination of an elastic with an inelastic part. The excitation gradient thus created is the *conditio sine qua non* for the segments' kinetic characteristics.

(2) An elastic bandage alone, or an inelastic bandage alone produces no kinetic effects whatsoever, regardless of the mode or duration of application.

(3) Experimental and clinical observation has shown that the elastic part of the segment becomes the kinetically facilitating field, the inelastic part the kinetically impeding field.

(4) Facilitation and impedance respectively of antagonistic muscle groups occur in a reciprocal pattern.

(5) The reciprocal pattern is, however, reversible by reversing the orthokinetic fields. (See photographic series.)

(6) No orthokinetic effects can be obtained on extremities with partial or total loss of sensory function of the skin surface, even if motor function remains or is intact.

(B) *Muscle Power and Joint Range.*

(7) In cases *without* involvement of the "higher centers of transaction," increase of power in the facilitated muscle group occurs as a rule *immediately* or almost so, delayed on occasion, not at all very rarely.

(8) Likewise, restoration of power is usually *total* or almost so, partial, minimal or zero only rarely. Both immediacy and totality are apparent and seem almost predictable.

(9) In cases *with* involvement of the higher centers, gain of power by facilitation is sometimes immediate, often delayed or does not occur at all.

(10) Likewise, increase in power is either total, partial, minimal or zero. Both the time element and the degree of restoration are erratic and completely unpredictable.

(11) Range of motion increases directly proportional with gain of muscle power.

(12) After a normal or near-normal motor pattern has been re-established by orthokinetic (rotatory) exercises with the segments in place, experience has shown that such a re-acquired motor pattern is being *retained* even after the segments have been discarded.

(C) *Spasticity and Coordination.*

(13) Spasticity decreases in the impeded muscle group sometimes immediately, more often delayed. As with gain in muscle power, its disappearance may be total, partial, minimal or may fail to occur or,

(14) Spasticity may *shift* from the impeded to the facilitated muscle group in rare instances; it is important to note that the shift of spasticity is again (compare No. 5 above) *reversible* by reversing the orthokinetic segments.

(15) The greater the difference of spasticity between the agonist and antagonist, the better seems to be the potential orthokinetic result; the more equal the degree of spasticity, the more doubtful and difficult.

(16) Muscle coordination increases proportionately as spasticity decreases; thus, its res-

toration may be total, partial, minimal or zero.

(17) By the same token, coordination may occur immediately, delayed or not at all.

(D) *Relief of Pain.*

(18) This is a major feature of orthokinetic therapy. It has been encountered in the majority of cases in all categories—neurologic and non-neurologic alike, with or without involvement of the central nervous system, and frequently in a dramatically short time, also as a rule, either completely or with minor, often clinically insignificant residuals.

Comment

(a) The discovery in 1954 that an orthokinetic segment acquires true kinetic properties has now been confirmed time and again not only in our experimental work with normokinetic volunteers, but in 150 patients who have undergone orthokinetic therapy. The positive response of almost 80% to orthokinetics appears to be significant. It is even more so when we separate the cases with (higher level) involvement of the central nervous system from those without it. In the latter, the number of positive responses is 83% with 8% negative; in the former, the positive responses are 74% with 13% negative. (Even in the "questionable" category, the percentage of centrally involved cases is 13%, the centrally uninvolved only 9 per cent.)

(b) This difference re-emphasizes the commanding role of the higher levels of transaction, some details of which have been pointed out in the resumé. From the clinical point of view, it is of course distressing. It cannot distract from the fact, however, that it is indeed possible to manipulate the NMU—sensory receptor, motor respondent and muscle—with the innocently simple-looking orthokinetic segments in the overwhelming majority of dyskinesias of the periphery with intact higher central nervous system centers and, by the same token, even those with damaged higher centers, although obviously to a markedly lesser degree.

(c) That the elastic part of the orthokinetic segment actually becomes the facilitating field, the inelastic part the impeding, is demonstrated by the reversibility of the effects by reversing the orthokinetic fields. It is enhanced by the fact that spasticity disappears from the impeded muscle group and confirmed by the phenomenon of the shift of spasticity as well as by the fact that spasticity shift itself is *reversible* by again reversing the orthokinetic fields (resumé No. 14).

(d) Since the elastic portion of the orthokinetic segment is *always* and *without exception* the facilitating component, the inelastic portion always the impeding, the implication becomes rather compelling that there must exist an exteroceptor specificity such as claimed by Weddell,[9] namely that the receptors of Merkel and Meissner react to touch, those of Paccini to pressure. The clinical evidence gathered with orthokinetics would seem to support this view.

(e) Experimental and clinical evidence as well as newer results of research in neuromuscular physiology indicate that the prime mover in producing orthokinetic phenomena are the exteroceptors of the skin for the following reasons:

(1) The reversibility of facilitation and impedance respectively by reversing the orthokinetic fields, including spasticity shift.

(2) The exeroceptor specificity postulated above. A more detailed explanation for this will be given later.

(3) The refutation of the argument raised in the past of "general pressure." This is indeed, one might say, self-refuting since it rightly states that "when a muscle is encased in a tubular device it becomes impossible to differentiate between exteroceptor and proprioceptor excitation, since its general pressure excites (in all probability) both at the same time." This is indubitably true but actually misses the point because, first, the orthokinetic segment is not a tube, it covers often only half, in the larger muscles one third or less of the muscle mass (e.g., quadriceps—hamstrings). Second, the pressure is extremely delicate, which would make it highly questionable that its force was strong enough to cause the degree of muscle compression necessary to activate the muscle spindles, the primary proprioceptors. Third, even granted that this were possible this compressive force would have to compress the skin surface first, then the deeper layers of capillaries, connective tissue and subcutaneous fat, that is to say, those very layers which contain the exeroceptors *before* reaching the stimulation point for activating the muscle spindles.

This is obviously an anatomic impossibility.

(4) In addition, it should be kept in mind that the lighter the so-called pressure over the muscle, the better will be the potential orthokinetic results. This had already been observed by Julius Fuchs over 30 years ago, and has been confirmed by our work presently. (It is this very fact which caused Fuchs to "untighten" his tubular devices[5] and embark on his "modeling procedure.") This fact again seems to point to the exteroceptors as the originators of orthokinetic effects rather strongly. If the spindles were the prime movers, it would be difficult to understand why orthokinetic phenomena would become more pronounced, more visible under less pressure.

(5) Last but by no means least, there is the clinically observed fact that no orthokinetic effects have been produced when the peripheral sensorium of the skin is paralyzed, either experimentally by surface anesthesia or clinically while the motor function remained intact, or for example, in spasticity of the hemiplegic versus the spasticity of the transverse lesion of the cord. While the former, as has been pointed out, is responding well to orthokinetics in a great percentage of cases, the latter has been a complete failure, without exception. With the exeroceptor paralysis of the paraplegic, it seems, we are losing our chance altogether to manipulate the NMU via the periphery.

(f) If we then recognize the skin receptors as the "prime movers," it still is baffling to see a drop-foot brace discarded within a few minutes in a patient with multiple sclerosis when facilitating the pretibial muscle group; or see spasticity of 3 years' duration disappear in a hemiplegic forearm within seconds with wrist extension when impeding the flexor group; or, for that matter, the 2 new cases described earlier in this paper.

Thus, the immediacy and totality in "righting" motion belong to the outstanding characteristics of orthokinetics. The contention of most who have witnessed these phenomena is, I believe, justified that they are being caused not by ordinary, but by quite extraordinary reflex pathways, and that neither our common textbooks mention them nor do many workers in our field seem to be aware of them. The question then is whether there exists a specific function, or structure or both, connecting skin surface with underlying muscle in a direct specific manner as the clinical evidence of orthokinetics seems to indicate.

Skin Motor Areas and the Gamma Motor System

Hagbarth[10] has investigated reflex motor responses from the skin of the hindlimb of the spinal cat. The problem was whether ipsilateral extensor responses were really exceptions to the general rule of Sherrington,[11] the flexor response. Hagbarth found that both flexor and extensor responses could be elicited and in a definite structural pattern. For the knee, for example, the excitatory area for the flexor is to be found over the entire limb *except* in the skin overlying the extensor. This part of the skin is inhibitory for the flexor. Conversely, the excitatory area for the extensor is to be found *only* in the skin overlying the extensor; the rest of the entire limb is inhibitory for the extensor. In "mapping" this on the skin surface, there emerges a mirror symmetry or reciprocity of skin fields of excitation and of inhibition perhaps more clearly expressed as follows:

Motion of knee	*Skin area of inhibition*	*Skin area of excitation*
Extension	Remainder of limb	Over extensor only
Flexion	Over extensor only	Remainder of limb

Adding other pertinent facts, these findings can be enumerated thus:

(1) Both flexor and extensor responses were elicited ipsilaterally,

(2) And, not only by electrical and thermal, but also by *tactile* stimulation.

(3) They were obtained by stimulation of the skin itself.

(4) They were polysynaptic responses.

(5) These "skin motor areas" have nothing in common with the skin fields of distribution of the cutaneous nerves or with segmental arrangements.

(6) As to the cutaneous afferents, they are intermingled in both nerve stem and nerve root, so that an excitatory effect obtained from a certain point of the skin may be mixed with concealed inhibitory components and vice versa.

Apart from the necessity of a revision of Sherrington's rule, it appears that we are dealing here with an entirely *new organizational structure* within the skin revealing a most

intimate and direct connection between sensory afferents of its exteroceptors and muscle in a reciprocal pattern of distribution. We summarize with Granit:[12] "Hagbarth brought clarity into this field (of ipsilateral extension response) by proving that there was a definite functional connection between a muscle and the portion of the skin that covers it."

From the viewpoint of orthokinetics—technically, the application of gentle surface stimuli to the skin covering muscle—Hagbarth's skin motor areas have a strong, immediate appeal. Indeed, this has been so logical in its parallelism to the clinical experience and the discoveries in orthokinetics that I did not hesitate to predict, 2 years ago, the existence of skin motor areas in the cerebral human identical with, or similar to, those discovered by Hagbarth in spinal cats. This thesis has been criticized as "speculation without value." It is therefore particularly gratifying to report that of late, Hagbarth has come forth with laboratory evidence of that very fact.[13] It appears that accuracy of observation and deductive logic are still valid tools of clinical research.

While the discoveries by Hagbarth seem to account for an important sector of the afferent component of the NMU, another complex of studies concerns the muscle spindle, specifically the innervation, both efferent and afferent, of this principal proprioceptor of muscle.[12-16] What appears to be pertinent in this context, particularly as to Granit's "skin-muscle integration" and his gamma motor system, might be condensed here as follows:

(1) The spindle is not only excitable mechanically by change of muscle shape (tension, contraction, relaxation) but also neuroelectrically by direct motor innervation from the anterior horn of the spinal cord through the gamma neuron. It seems indeed that the gamma neurons represent the *exclusive* motor innervation of the intrafusal muscle fibers of the spindle while the alpha neurons innervate the extrafusal fibers only, i.e., the muscle at large.

(2) The spindle has 2 sensory afferents of its own, the primary from the nuclear bag, the secondary from the myotube region which seem to serve 2 different functions. The primary afferent has a direct (monosynaptic) connection with the alpha motor neuron (excitation of muscle at large) serving muscle contraction, what Granit has called "ignition system for alpha activity"; the secondary afferent of the spindle represents a mechanism responsible for reciprocally coordinated muscle action, i.e., extensor inhibition with flexor excitation simultaneously plus the "feed-back" of course to the spindle via the gamma efferent.

(3) In addition, and this deserves special emphasis, "efferent gamma activity was facilitated from the skin over the muscle and was inhibited from other areas," i.e., it is the gamma motor neuron which responds primarily to the sensory afferents from the skin motor areas of Hagbarth.[17] This, in turn, excites the muscle spindle leading to "alpha ignition," hence to muscle contraction at large.

(4) Since we are dealing here with a most intimate integration between the activities of gamma and alpha motor neurons (among other integrative features), a brief summary of the differences between the two is, I think, appropriate:

(a) Gamma fires the intrafusal muscle fibers, alpha the extrafusal = muscle at large.

(b) Gamma "ignites," via spindle and its primary afferent, alpha.

(c) Gamma is the *primary* respondent to skin motor area excitation.

(d) Gamma has both a lower excitation threshold and a lower conduction velocity than alpha.

(5) Finally, it should be mentioned that other proprioceptors are involved in the totality of the NMU, particularly the Golgi tendon organs the afferents of which carry inhibitory impulses to both alpha and gamma neurons.

Summary

These newer and newest discoveries, it seems, provide new and clearer insight for understanding motor phenomena. Outstanding among them appears to be the vital commanding position of the gamma neuron and the muscle spindle and their functions, comparable—as Granit has hinted at—to the electrical system of a motor car. It seems as though they were a combination of generator, transmitter, distributor, modifier and ignition

system for a great number of varied and variable impulses and motor actions.

Another striking fact is that skeletal muscle seems to be under the influence of 2 motor systems, the gamma system as the real generator, the alpha system as the "executor" of motor "commands"; plus the "feed-back," mechanical as well as electrical, to the spindles and their afferents, a peculiar, obviously most effective mechanism for a continuous cyclical stream of impulses from muscle to cord and vice versa: a self-regulatory mechanism within the periphery for uninterrupted adjustment to outside conditions and demands.

Last but not least, there is the exeroceptor position, now stated—from the viewpoint of orthokinetics in particular—with assuring clarity and logic, that they are "grouped" as it were, within dynamic functional "fields," the skin motor areas, directly connected with gamma neurons, themselves the vital component of Granit's gamma motor system. I sincerely believe that Hagbarth's work is the key indeed to the understanding of orthokinetic effects. As Granit has expressed with classical simplicity: "Skin and muscle are functionally integrated so that muscle is excited by stimuli within its own skin area." In this, it seems, we have the principal and fundamental answer to our quest.

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Ulcerative Colitis in Children*

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The problem of ulcerative colitis in childhood is a distressing one. Every attempt is made to manage such cases medically, but surgical treatment becomes imperative under certain circumstances.

ACUTE AND CHRONIC NONSPECIFIC ULCERATIVE COLITIS remains an enigma to the medical world. The etiology is certainly not clear.[1] It has been the subject of extensive investigations concerning infection by various microorganisms or food allergies,[2] enzymatic digestion of the colonic mucosa by lysozyme,[3] severe emotional disorders,[4] and most recently, immunologic mechanisms in the form of autoantibodies.[5]

For many years it had been considered a disease almost restricted to the young adult. However, in 1923, Helmholz[6] reported its occurrence in childhood, and in 1940, Jackman, Bargen and Helmholz[7] called attention to its more frequent place in the serious diseases of the child. Since that time Kirsner and associates,[8] Lagercrantz,[9] Meeker and Goff,[10] and others have presented significant series from various parts of the United States and Europe testifying to ulcerative colitis affecting younger age groups. This disease is certainly not a scientific curiosity when it occurs in children, and its diagnosis should be suspected whenever syndromes of colonic mal-activity present themselves.

Probably the youngest documented case has been seen at the age of 3 months,[11] but the condition more commonly begins at about age 7 and is most prevalent just before puberty. Girls seem slightly more prone to this affliction than boys, and the white race much more than others. In England, children of Jewish ancestry are in the majority.

Signs and Symptoms

Ulcerative colitis makes its appearance in children much as it does in adults. It may be fulminating, moderately rapid, or insidious. There is one difference, however. Once the process is established and the diagnosis confirmed, it tends to be uniformly severe and requires vigorous treatment. The many mild cases of ascending proctitis and recurrent hyperactivity of the bowel with essentially normal colonic barium roentgenograms seen in adults do not frequently occur in children.

It is often ushered in by some concomitant infection as pharyngitis, acute gastroenteritis, even rheumatic states, so the definitive diagnostic procedures of sigmoidoscopy and barium enema are postponed or not even thought of, and the final diagnosis is in masquerade for weeks.

Diarrhea is common but may not be present at first. In fact constipation accompanied by the passage of small amounts of bloody mucus may be an early sign. Later, however, all patients will develop colonic hyperfunction. Fever is not an early sign except in rapidly progressing cases, though most children will have a tachycardia. Cramping is encountered in a majority of instances but may be completely absent, particularly in those whose early signs are the passage of blood.

Diagnostic Procedures

The common denominator of diagnosis of all colonic disturbances is sigmoidoscopy and it should be used early. It can be performed on children simply, quickly, without trauma, and without anesthesia by one familiar with its everyday use. Normally, we urge the daily diagnostic use of this instrument by all practitioners. However, in this instance, the borderline changes such as mucosal edema, redness, early friability, and beginning granular sheen must be not only recognized but also interpreted. Therefore, whenever possible, this examination should be performed by one with training and experience in these fine points. Of course, in severe or fulminating cases of ulcerative colitis, the massive destruction, purulent patches, and inflammatory islands of

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polypoid mucosa, are so striking that anyone who can pass the instrument can make the diagnosis.

All children do not have severe rectal involvement and it is most important to visualize the sigmoid. Because of the shortness of the rectum and sigmoid in this age group, it can usually be accomplished with a 25 cm. scope having a one-half inch caliber barrel.

Stool studies should be carried out in search of *Entamoeba histolytica* and salmonella bacteria. The latter infection is more commonly confused with ulcerative colitis in its sigmoidoscopic appearance. The presence of numerous pus cells, red blood cells, and Charcot-Leyden crystals is very common.

The barium enema is very helpful in the early stages of ulcerative colitis in determining its extent throughout the remainder of the colon. The roentgenologic changes are apt to occur earlier in children than in adults and therefore the barium enema plays a definite role in the diagnosis.[12] The changes present a feathery appearance indicating destruction of the mucous membrane (Fig. 1); narrowing and shortening of the bowel; polypoid hyperplasia (Fig. 1); and a cobblestone appearance on expulsion (Fig. 2). In very severe cases, particularly in patients having generalized toxemia, patients may present a dilated sac-like colon on barium enema (Fig. 3).

FIG. 1

Feathery appearance and shortening of the bowel.

FIG. 2

Cobblestone appearance on expulsion film.

Treatment

We believe in the early and vigorous treatment of ulcerative colitis both in adults and children. This is particularly true in the children because most cases will proceed to the moderately severe or severe category.

This disease is emotionally exhausting, physically crippling and sometimes fatal. For these reasons, all children who are suspect of this condition should be hospitalized for thorough diagnostic study and early treatment in an institution whose pediatric medical and surgical facilities are adequate to cope with this serious problem.

Once the diagnosis has been established all modalities of medical treatment should be used when indicated. Since steroids have seemed to be the single most effective medical weapon, we believe they should be used early and ade-

FIG. 3

Toxic colon with a sac-like appearance.

quately in all cases of ulcerative colitis and not reserved for trouble spots.

Formerly, in the treatment of this disease we used ACTH, both in children and adults, but in the past several years we have used steroids by mouth with no difference and with much more convenience. The chemically modified adrenocortical steroids can be used in higher doses with minimal electrolyte changes. Prednisolone (delta'-hydrocortisone) is begun in doses of 15 milligrams daily and increased by daily 5 milligrams increments to an approximate daily dose of 40 milligrams. This is maintained for about 7 to 10 days and then reduced 5 milligrams per day to a maintenance dose of 15 to 20 milligrams for a long period. The continuance of the steroids depends on the sigmoidoscopic appearance of the rectal and colonic mucous membranes at weekly intervals.

The antispasmodic, homatropine methylbromide (Malcotran) seems well tolerated and can be given up to 30 to 40 milligrams daily without side-effects of mouth dryness, visual disturbances and urinary retention. It is not used in cases where there is evidence of atony of the colon. Paregoric remains an effective drug to control diarrhea and is used routinely where that is a symptom.

Sedation does not seem as much a problem in children as in adults. When it is necessary, the use of 200 milligrams of meprobamate three or four times daily seems effective. Barbiturates are used sparingly but the commercial addition of one-eighth grain of phenobarbital to the homatropine methylbromide is permitted.

Whole blood transfusions in repeated small amounts are used to combat secondary anemia when it is present, and iron in a tolerated form is given when the intestinal activity becomes quiescent. Broad spectrum antibiotics are not used routinely unless there is evidence of sepsis as shown by elevation of temperature or increasing abdominal tenderness. Chloramphenicol is the drug of choice because of its wide spectrum of action and its known freedom from the complications of diarrhea due to change in colonic flora.

Extensive dietary regulations are difficult to impose on children who are seriously ill, and very little attempt is made to establish elaborate diets. Dairy products, condiments and fruit juices are about all that are avoided.

Psychiatric Aspects

It is our impression that the emotional element in children with ulcerative colitis is more prominent than in adults. However, this may be explained on the basis of our willingness to accept quite different behavior patterns in adults as a normal part of their developed personalities, whereas our concept of children is quite stereotyped. We are less likely to view slight departures of behavior as being within normal. Be that as it may, the use of psychiatric consultation and treatment is welcome because the results of modern medical, chemical and surgical treatment of ulcerative colitis leaves much to be desired.

But the practical answer is, where does one obtain the extensive and expensive psychiatric care necessary, if we are to use this modality of therapy? It cannot be "one-shot" any more than the administration of steroids be one day or one week.

Indications for Surgery

The primary indication for the use of surgery is the imminent loss of a life. This is threatened in perforation, continued hemor-

rhage, and intestinal obstruction. Procrastination in these emergencies is foolhardy.

Secondary indications for surgical intervention are the development of the extra-colonic ravages such as arthritis, and cessation of development, particularly at the age of puberty.[13] Severe anorectal complications of rectovaginal fistula, recurrent abscess formation, particularly when it threatens rectal continence, are also indications for surgery.

A third indication for surgery is the knowledge of the statistical incidence of carcinoma developing in chronic subacute ulcerative colitis of long duration. Careful study of necropsy material indicates this to be as high as 15 per cent.[14] However, clinically it is about 3% in an over-all survey of 6,890 patients.[15] This compares favorably with 4.4% in Lagercrantz's[9] series of 129 children, and 4.3% in 115 children reviewed by Svartz.[16] These and other concrete evidence of this possibility makes one pause and reflect. This is particularly true when it is realized that all these carcinomas in the children series occurred at or before the age of twenty-one. Carcinoma of the colon and rectum is almost nonexistent in this age group under ordinary circumstances and an incidence of 3 to 4% is even more startling than the figure sounds.

On this statistical ground alone, all other factors being under control, the performance of ileostomy and colectomy is certainly open to much argument and question. However, when added to some other uncontrolled aspect of the disease, it must be considered.

Operative treatment should include ileostomy and colectomy. Whether or not the rectum is left behind depends upon the degree of disease and the thoughts of both the surgeon and the parents. Certainly the coldest of us cannot blithely claim that an irretrievable sentence to life-long ileostomy is a simple cure for this dreadful disease when it afflicts a child.[17] Who is there among us who does not harbor the hope and even the confidence that in our time the key to this inflammatory killer will be found. This hope and recent experiences in ileorectal anastomosis must be in our minds when we decide on the fate of a child to be treated surgically for ulcerative colitis.[18,19] Under no circumstance, however, can philosophic treatises influence us when we are actually confronted with leaving a rectum in the face of immediate or early danger to the patient.

The technic of the operation in children differs little from that in adults. Care must be made in advance to place the ileostomy where the appliance will not interfere with the umbilicus, belt line, or superior anterior iliac spine, as there is not much room for error in a child. We believe that all colostomies and ileostomies should be made flush and with a mucocutaneous fixation. This fixation is made by about six to eight interrupted 4-0 chromic sutures which pass through the skin edge, the serosa about one-eighth inch from opening and the mucosa, and then are tied.

The pelvic dissection, particularly the removal of the rectum, is a little more tedious in the child, due to the thinness of Denonvilliers' fascia in the male and the rectovaginal septum in the female. This technical difficulty is a little more pronounced when there is perirectal inflammation. As a result the danger of rectourethral fistulas in the male must be considered when the rectal stump is left behind.

It is not within the scope of this presentation to outline the careful and minute postoperative care necessary in major surgery in the child except to repeat that elective, serious procedures are better cared for in institutions with adequate pediatric technicians and equipment.

Illustrated Cases

Case 1. K. P., a 7 year old girl, was stricken with painful ankles, fever, gastroenteritis, and a diagnosis of rheumatic fever was made. Four weeks later the fever had subsided but diarrhea persisted and *Entamoeba histolytica* in the stool was reported. Despite adequate antiamebic therapy with Diodoquin (diiodohydroxyquinoline), Milibis (glycobiarsol), and finally emetine, no improvement in the diarrhea occurred and she began to pass large amounts of bloody mucus.

Sigmoidoscopic examination revealed the typical picture of ulcerative colitis, and ACTH and cortisone were administered; the symptoms subsided. Medication was withdrawn and 6 months later she developed severe acute arthritis of the large joints, colonic bleeding and evidence of peritonitis. Conservative measures were used including broad spectrum antibiotics and gastric intubation and the abdominal symptoms subsided. The arthritis did not. The family refused operation at this time. One year later she had not grown an inch or gained a pound. Multiple perianal abscesses and a rectovaginal fistula developed.

An ileostomy and partial colectomy were performed and she recovered well. Her arthritis disappeared in 4 months and she again began to grow normally and gain weight. Four years have elapsed since the onset of the disease and about 3 since operation. The child

is living a normal life, attends school, but the rectovaginal fistula persists.

Comment. This case illustrates the confusion that often attends the diagnosis of ulcerative colitis in children. Whether or not the child actually had amebiasis is open to question. However, acquired infections as well as such opposites as "mycin" colitis all have been known to trigger chronic ulcerative colitis. She also points up the frequent lack of growth that accompanies this disease.

Case 2.* S. F., a 12 year old physician's daughter, began having watery diarrhea which soon became accompanied by bloody mucus. She was treated by hospitalization, blood transfusions and steroids, but went progressively downhill. A little over one year from the onset of her disease she underwent ileostomy and an almost total colectomy. The rectum was left in place. The immediate course was good and she adjusted well to the ileostomy and began to gain weight. Five months later, however, severe multiple arthritis occurred and re-examination of her rectal stump revealed it to be the site of active disease. It was removed and the arthritis cleared up almost at once. The child is well today.

Comment. This case illustrates the extracolonic complications of arthritis and is an example of this type of complication recurring in the presence of even a small focus of the disease.

Case 3. S. F., a 9 year old girl, began to have increase in stools to five or six daily in January 1959, with no other symptoms. She was examined by several pediatricians in her home area and was diagnosed as having food allergy. Extensive tests were carried out, and strict exclusion diets were instituted to no avail. In July 1959, the increase in bowel activity had not changed, but began to be accompanied by occasional bloody mucus. She was referred for further study and hospitalization. Sigmoidoscopic examination revealed a mucous membrane that was extremely friable and bled rather easily when stroked with the end of the scope. All stool studies were normal and a diagnosis of early ulcerative colitis was made.

She was treated with steroids at once, dexamethasone .75 mg. 3 times daily and other supportive measures including chloramphenicol were used when she developed fever. The bloody mucus subsided and she began to have one to two stools daily. She developed a severe "moon-face" and gained 15 pounds suddenly, and therefore the steroid was carefully withdrawn.

The child did well until May 1960, when sigmoidoscopy showed granular mucous membrane with ulcerations and bloody mucus. Steroids were begun again; this time on prednisolone, 15 mg. daily, and she has been maintained on approximately this dosage to date, changes in dosage being indicated by the sigmoidoscopic appearance of the mucous membranes at examination every two or three weeks. Her growth and weight have continued to be normal.

Comment. This is an example of the insidious nature of the development of this disease and also its long-term management with continuous administration of steroids. What the future of this child holds, I have no idea and I doubt if anyone else would predict. As to how long the drug can be continued here and in other cases, one can only say it has been used for 30 months continuously without ill effects.[20]

Case 4. D. P., a 14 year old girl, suddenly began to have severe diarrhea in February 1959. Attempts to control her symptoms were futile and no definite diagn sis was made. She was referred to our city for further care. She was a very obese, dull child. Shortly after admission she began to bleed seriously and 7 pints of blood were used as replacement. Sigmoidoscopic examination showed a relatively normal rectum but inflammatory changes began in the mucous membrane of the rectosigmoid and became very much worse in the lower sigmoid, producing large areas of denuded mucous membrane and purulent patches.

Before any definite regimen of drugs could be decided upon and be established, she developed abdominal distention, fever to 104°, and evidence of colonic perforation with roentgenograms showing free air in the abdominal cavity. The patient was almost moribund, and was treated conservatively with antibiotics and intestinal intubation for 48 hours. She improved sufficiently to consider emergent and desperate surgery.

An ileostomy and colectomy to the midsigmoid was carried out. At operation a large abscess in the area of the hepatic flexure and another in the pelvis were present. These were drained. There was also generalized peritonitis. She expired 12 hours after operation. Postmortem examination showed the same findings which were present at operation with the exception that the abscess cavities had been drained.

Comment. This is an example of the vicious nature of the fulminating type of this disease. A brief resumé of such a case does not begin to recount the hours spent, the laboratory procedures, the heroic administration of drugs that were packed in the several days that told this story.

Case 5. R. S., a 12 year old boy, had an established diagnosis of ulcerative colitis made at age ten. For the past 2 years he has had numerous remissions and exacerbations while on a variety of steroids, including ACTH, cortisone, and prednisolone. Intermittently sulfa derivates and other broad spectrum antibiotics were administered. He would improve remarkably while in the hospital and become ill a short time after returning home. All attempts at psychiatric investigation could not point to any definite emotional difficulties in his home life, other than that his mother had died about 4 years prior to the onset of his disease and that his father had remarried.

On his most recent admission during an exacerbation, extensive polypoid changes were seen sigmoidoscopically from the rectosigmoid upward. If one had

*We are indebted to Doctor H. Clinton Davis and Doctor William Shaver for inclusion of this case.

not known the past history a diagnosis of childhood polyposis might have been made. Because of this sudden marked change in the nature of his disease an ileostomy and colectomy was performed. A four to five inch rectal segment was left in place and he has responded well and is living a normal life.

Comment. This case illustrates an indication for surgery in an instance where immediate life was not in danger but in which a secondary change had occurred which could be the precursor for a later malignancy. The technical possibility for a later anastomosis is present if his rectal stump remains free of disease.

Comment

These cases do not necessarily illustrate the usual course of ulcerative colitis, but were deliberately selected to show different problems that present in the management of this disease. The motivations and aims may not always be the same in children as in adults. We hope they illustrate the many faceted situations that require different approaches. We do not believe that evidence supports any sole medical therapy or any specific operation at this time, other than the concept that ileostomy alone offers very little.

Summary

1. Attention is again called to the occurrence of ulcerative colitis in children as not being a rare entity.
2. Signs and symptoms and diagnostic procedures of this disease have been presented.
3. A broad method for the medical care of childhood ulcerative colitis has been offered.
4. Indications for the surgical treatment have been outlined.

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Discussion (Abstract)

Dr. Alejandro F. Castro, Washington, D. C. I am happy to comment on this excellent paper by Dr. Matthew Larkin. He has covered the subject well and illustrated the difficult problems that face the abdominal surgeon in cases of chronic ulcerative colitis, particularly in children.

I doubt there are any marked differences between the disease as it affects adults or children. I believe the difference is in the psychologic approach the surgeon has to a child ill with chronic ulcerative colitis. There is more reluctance in performing ileostomy and colectomy in a child than in a young adult, consequently surgical treatment may be delayed in some cases. Dr. Larkin has brought out the need for earlier surgery in these children, and hinted that the rectum can possibly be saved in a good number of them. This, of course, would and will open the field to ileorectostomy in many cases now being treated medically because of reluctance on the part of the parents, the child, or even the pediatrician involved to subject the patient to a life with an ileal stoma. This would also decrease the danger of cancer of the large bowel in these children. It is well to note that cancer occurs more readily in patients with ulcerative colitis treated medically even though objectively and subjectively the patient seems to have recovered from the ulcerative process.

Of 77 operative cases in our files only 15 (20%) were younger than 20 years of age. Most of these were between 13 and 16 years old. Two were below the age of ten.

I am of the same opinion as Dr. Larkin that the early diagnostic changes of ulcerative colitis in children may be missed by the casual observer. One of the first things we have noted is the disappearance of the submucosal vascular pattern. This, of course, is due to edema and hyperemia of the overlying mucous membrane. It takes a trained sigmoidoscopist to detect these early changes.

To the medical treatment outlined by Dr. Larkin, I would like to add the use of Azulfidine. We, and also our colleagues in Washington, have had excellent

and striking results in several patients. If this drug is effective, the need for cortisone and similar compounds is postponed or, as in some of our cases, obviated.

To the indications for surgery outlined by Dr. Larkin, I would like to add further support to colectomy in cases of failure in growth and apparent endocrine imbalance. When this occurs these children are seriously ill and usually will not thrive unless the colon is extirpated.

There are three things to my way of thinking that have made surgery more tolerable and drastically decreased surgical mortality. One, and the most important, is simultaneous ileocolectomy removing most or all of the diseased bowel. Ileostomy alone, subject to the high mortality of past years, has practically been abandoned. Two, is the mucocutaneous suture described by Dr. Larkin which prevents malfunction of the ileal stoma; and three, the mutual aid these patients get in the now popular ileostomy clubs. They realize they are not the only one with an artificial anus.

As to the psychiatric help for these patients, I would like to state that once chronic ulcerative colitis is well established the aid psychiatry has given our patients is minimal. On the other hand, in the early stages of the disease psychiatry may be quite helpful.

Dr. William Davis, Jr., New Orleans, La. It is a real pleasure to participate in this discussion. My comments are based on a review of the 22 cases of ulcerative colitis in children that we have seen during the past few years at the Ochsner Clinic; 18 of these were observed after steroid therapy had become available. Seventeen had severe ulcerative colitis; of the 14 treated medically, 9 responded satisfactorily and did not have recurrences. Six required colectomy and ileostomy; 5 of these are presently in good health, and the results are considered to be excellent. The other, a 12 year old boy of extremely over-protective parents, who seemed unable to cooperate in any program of treatment, finally was forced to submit to colectomy because of continued malnutrition, loss of weight, and diarrhea. He had idiopathic cardiac hypertrophy and had previously had cerebrovascular thrombosis. His death shortly after operation was attributed to cardiac arrest. Permission for necropsy could not be obtained.

The significant factors that emerged from study of these cases were: (1) the uniformly severe nature of ulcerative colitis in children, with its damaging interference with normal growth and resultant dwarfism; (2) the fact that with vigorous treatment remission can frequently be obtained but continued well-being is jeopardized by ever present important intra-family psychopathologic relations, the parents usually being much sicker psychiatrically than the children, unless the parents as well as the children are treated. We agree with Dr. Larkin and with previous discussers that psychotherapy is of little or no benefit during an acute attack, but it has been my experience that remissions can be maintained if the family can participate in the treatment. Many of our patients seemed to be intelligent children and, perhaps therefore, more keenly aware of environmental problems than some of their less able companions.

I would like to emphasize that the golden opportunity for cure of this disease is during the initial acute attack and I would urge an extremely vigorous approach to treatment at this time including immediate and relatively large doses of steroids, Azulfidine in maximal tolerable dosage, usualy 1 to 1.5 Gm., 4 times a day, an anticholinergic drug of choice for relief of cramping and help in prevention of diarrhea, a mild sedative, such as meprobamate, as has been mentioned by Dr. Larkin, and one of the hydrophilic colloids, such as Konsyl (one teaspoonful once or twice daily in a full 8 ounce glass of water). We restrict diet only moderately as far as roughage and seasoning is concerned, it being our belief that caloric ingestion, particularly protein, is much more important than specific exclusion of any types of foods. We usually permit milk, which is ordinarily well tolerated.

On this program prompt remission is most frequently accomplished and, when obtained, ordinarily leaves relatively little scarring and fibrosis, a condition which we believe minimizes the chance of recrudesence of the disease. On the other hand, if after a few days of intensive treatment of this sort, considerable improvement does not occur, we believe that surgical intervention is indicated.

One further point that I should like to emphasize is the extreme usefulness of rectal mucosal biopsy in establishment of the diagnosis of ulcerative colitis when the gross mucosal changes are minimal; frequently, resort to microscopic examination will often result in much earlier diagnosis and concomitant early, vigorous and likely more successful treatment.

CASE REPORT

Soft Tissue Calcification in an Extremity Due to Metastatic Carcinoma of the Colon

ALFRED SCHICK, M.D., *Clearwater, Fla.*

IN THE RECENT LITERATURE there have been several reports of malignancies of the gastrointestinal tract, showing calcifications in either the primary lesion or the intraperitoneal metastases.[1-5] The case to be presented is unusual in that the metastatic lesions containing calcium were located in the soft tissues of the extremities and it was these lesions which first prompted the patient to seek medical aid.

Case Report

The patient, a retired 67 year old white farmer, was in excellent health until about 4 months prior to admission, when he noted a feeling of discomfort in his upper abdomen. This was not associated with any change in the pattern of his bowel movements, nor with any vomiting or change in appetite. He did not notice any weight loss. Approximately 2 months prior to his admission he noted a painless swelling in the right deltoid region and also the appearance of a small nodule in the abdominal wall, for which he sought medical advice.

Physical examination at that time showed a firm mass approximately 5 cm. in size in the right deltoid region, which appeared fixed to the underlying muscle. There were several subcutaneous nodules in the abdomen and a hard mass could be palpated in the midabdomen at the umbilicus.

A biopsy of the mass in the deltoid region was performed and was reported as metastatic adenocarcinoma. The patient was then admitted to the hospital for further study.

Physical examination on admission showed a healing biopsy scar in the deltoid region. Several movable but firm subcutaneous nodules were present in the abdominal wall. A nodular, firm mass, approximately 5 cm. in its widest diameter was palpated deep in the abdomen. Rectal examination was negative. A stony hard, nonmovable mass was present in the left thigh. The patient stated that this had appeared since the time of his first biopsy.

Laboratory findings were within normal limits except for a moderately severe anemia with a Hgb. of 8.8 Gm. per cent.

X-ray studies showed the lungs to be free of metastases. The upper gastrointestinal series showed a clover-leaf deformity in the duodenal bulb. A barium enema revealed a napkin-ring constriction in the transverse colon, ulcerated in its center (Fig. 1). Radiographs of the femur showed a soft tissue mass containing a faint deposit of calcium adjacent to the femur (Fig. 2). The cortex of the femur was slightly thinned but no definite bone invasion was noted.

The radiologic impression was: (1) carcinoma of the colon; (2) malignant tumor in the thigh, representing possibly a fibrosarcoma or an unusual metastases of the

FIG. 1

A constricting ulcerative lesion is present in the midtransverse colon.

FIG. 2

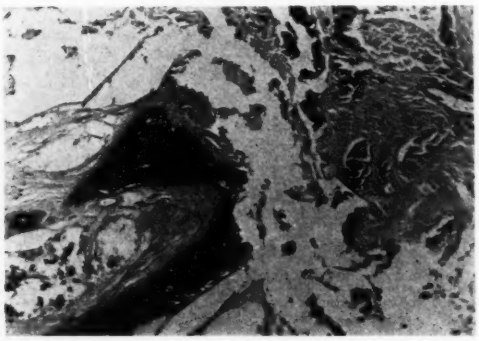
Left femur (lateral view, soft tissue technic). Soft irregular calcifications are adjacent to the femur; very minimal thinning of the cortex adjacent to it.

colon; and (3) duodenal deformity due to healed peptic ulcer.

At laparotomy a large carcinoma of the transverse colon was found. Invasion of the mesocolon was present and enlarged periaortic nodes were plentiful. The primary lesion was excised and an end-to-end anastomosis was performed to relieve a low grade obstruction already present. At the same time a biopsy was done on the lesion of the thigh.

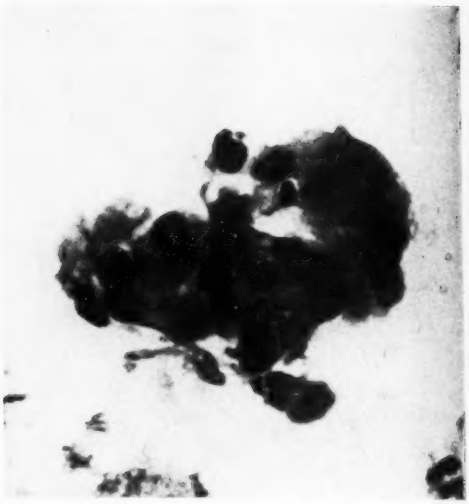
The pathologic report on the primary lesion was:

FIG. 3



Photomicrograph of biopsy specimen from left thigh (low power). The area of ossification is on the left; tumor cells are on the upper right, and on the lower left-hand portion of the field.

FIG. 4



Photomicrograph of biopsy specimen from left thigh (high power) showing the anaplastic tumor cells.

Glandular tissue with moderate variation in cells. Mucin is secreted by many of the cells. The neoplastic tissue blends through the muscularis and adventitia into the surrounding fat. The report on the biopsy specimen was: Fibrous connective tissue with necroses and calcification. Scattered nests of anaplastic cells are seen. Some striated muscle fibers are present (Figs. 3 and 4).

Discussion

In the recent literature there have been a number of papers dealing with calcifications in malignancies of the gastrointestinal tract.[1-5] These calcifications were noted both in the primary and intra-abdominal metastatic lesions. These malignancies, as in the case presented, were all mucinous adenocarcinomas. The fine, striated calcifications in the lesions are thought by some authors[2,4] to be sufficiently characteristic to permit a preoperative diagnosis of adenocarcinoma.

The calcification in this case was similar in appearance to that described in the literature, and would certainly be regarded as highly suspicious of metastatic carcinoma even if the primary were not known.

Summary

A case of carcinoma of the transverse colon has been described, in which the metastatic lesions in the extremities were the first signs of the disease. These lesions contained cal-

cium in a rather characteristic pattern, visible on the radiograph. To the best of my knowledge, this is the first case of this type reported.

323 Jeffords Street

Acknowledgment

Grateful acknowledgment is made to Drs. W. L. Williams and J. B. Leonard of the Departments of Pathology of Mercy Hospital, Charlotte, N. C., and Morton F. Plant Hospital, Clearwater, Fla., respectively, for the selection and preparation of the pathologic material used to illustrate this paper.

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TELEVISION IN DALLAS

Southern Medical Association will present a varied schedule of TV programs in Dallas during its Fifty-Fifth Annual Meeting, November 6-9. Dr. Cecil G. Yarbrough, Dallas, is Chairman of the TV Committee for the Dallas meeting.

Smith Kline & French Laboratories and Merck Sharp & Dohme will produce the presentations. Response to television at previous Association meetings has been quite favorable.

Smith Kline & French has planned a full schedule of closed circuit scientific color TV shows to be screened at the Dallas Memorial Auditorium. The scientific sections which have planned to utilize these facilities include: Gastroenterology, Gynecology, Medicine, Obstetrics, Ophthalmology and Otolaryngology, Pathology, Plastic and Reconstructive Surgery, Proctology, Radiology, Surgery, and Urology.

Merck Sharp & Dohme will present a public telecast over a commercial channel. This telecast is a part of the MSD Postgraduate Program. MSD, through the Postgraduate Program, supplies funds for various projects in support of postgraduate medical education, including lectures, courses, medical research conferences, television, surveys, seminar reports, and the *Merck Manual*. Last year, during SMA's Fifty-Fourth Annual Meeting in St. Louis, MSD presented "A School for Doctors," showing how community efforts by doctors and other citizens brought about the University of Kentucky Medical Center.

Alternating Hypertropia*

A. D. RUEDEMANN, JR., M.D., *Detroit, Mich.*

DURING THE PAST FEW YEARS there has been much discussion about the *A* and *V* syndromes. Urist[1] apparently began this about 1951. His main point was the high number of horizontal squints with secondary vertical deviations. Urist pointed out the difference in the angle of deviation of the horizontal squint which occurred in the up and down positions. His thesis has been that the horizontal and not the vertically acting muscles are responsible for this defect.[1-7]

Costenbader[8] named the syndromes A and V in 1955. Since that time the fine work of Knapp,[9] Miller,[10,11] and others have added to our understanding of these extremely interesting problems in binocular coordination.

I must be frank to admit that it has been only recently that we have added the terms A and V to our definition of these cases.

Herein lies our tale, for it is at this point that our evaluation of these cases has followed a slightly different course.

By way of review, the A and V syndromes might be classified as follows:

V Syndrome 1. *Exo* greater looking up
Convergence insufficiency (?)
2. *Eso* greater looking down
Convergence excess

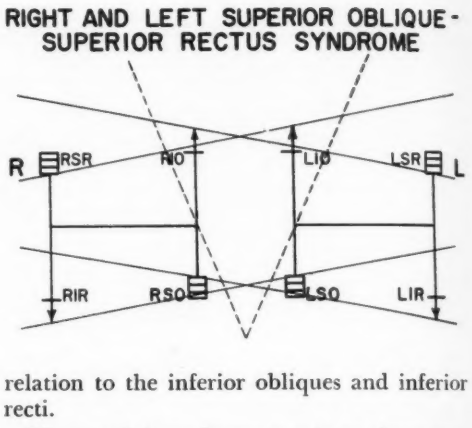
A Syndrome 1. *Exo* greater looking down
Divergence excess (?)
2. *Eso* greater looking up
Divergence insufficiency

In alternating hypertropia, either esotropic or exotropic, with alternate overaction of the inferior obliques, the horizontal deviation is greater looking up if exotropic, or greater looking down, if esotropic (V syndrome).

It has been our custom to classify these cases of alternating hypertropia as: *Right and left superior oblique—Superior rectus syndrome* (Fig. 1).

In cardinal positions there is underaction of the superior recti and superior obliques in relation to the inferior obliques and inferior recti.

FIG. 1



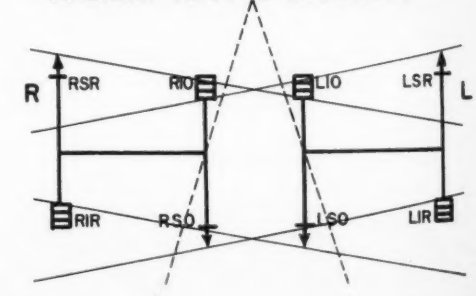
The usual A syndrome case is an alternator, either exotropic or esotropic, with alternate overaction of the superior obliques. The horizontal deviation, if esotropic, is greater looking up. The horizontal deviation, if exotropic, is greater looking down.

It has been our custom to define such cases as: *Right and left inferior oblique—Inferior rectus syndrome* (Fig. 2).

In the cardinal positions there is underaction of the inferior obliques and inferior recti in relation to the superior obliques and superior recti.

This method of analysis is not new. To my

FIG. 2



*Read before the Section on Ophthalmology and Otolaryngology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

knowledge it was introduced by Owens[12] at the Wilmer Institute in the late 1940's and by Ruedemann.[13]

Proper evaluation of the eyes in the cardinal positions of gaze is essential to diagnosis. The patient's head must be maintained in an erect position. The patients notoriously assume their abnormal head-body posture to achieve binocular parallelism. This must be prevented. Erect posture, no head tilt, face turn, or chin elevation or depression can be allowed.

Slow screening of the eyes is very beneficial to diagnosis. Even though these patients are alternators, they generally prefer fixation with one eye under normal conditions. Prolonged occlusion of the usually fixing eye may be necessary. Any evidence of double hypertropia should be noted. Diagnosis of these cases is aided by repetitive examination.

Treatment

Before discussing the treatment utilized in these cases it is essential to understand the analysis noted above.

V Syndrome

The hypothetical development of the V syndrome could be as follows:

1. (Fig. 3) Right eye fixing, there is overaction of the *left inferior oblique* with consequent over-elevation in the up and right position. Associated with this would be a relative under-elevation of the *right superior rectus* in the same position. In the down and right position there would be a relative underaction of the *left superior oblique* and a relative overaction of the *right inferior rectus.*

FIG. 3

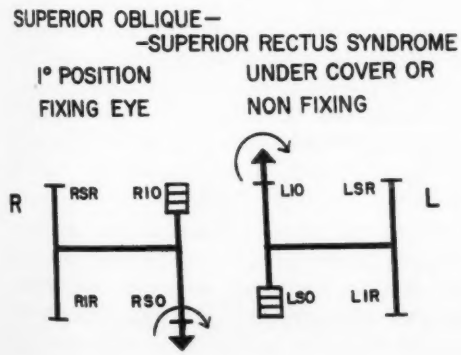
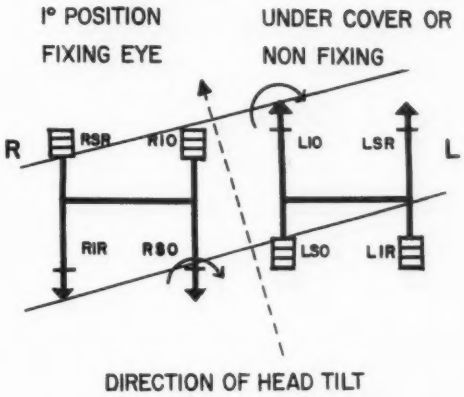


FIG. 4



The overaction of the *left inferior oblique* causes an excessive excyclotorsion of the left eye which must be balanced by an incyclotorsion of the right eye. This means there will be a head tilt to the right.

The incyclotorsion of the right eye for ocular parallelism means that there is relative overaction of the *right superior oblique* with underaction of the *right inferior oblique.*

2. The result of this is seen in figure 4, right eye fixing. In addition to the above there will be an additional underaction of the *left inferior rectus* down and left and an overaction of the *left superior rectus* up and left.

3. When the opposite eye is forced to fix, the exactly opposite picture will occur (Figs. 5 and 6).

4. The summary of cardinal positions (Fig. 7) brings us to the full-blown clinical picture (Fig. 8).

According to Krewson's vector analysis, the inferior oblique passes anteriorly to the

FIG. 5

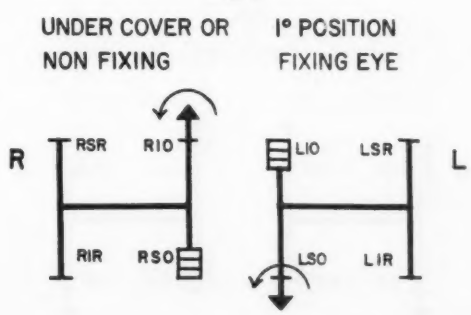
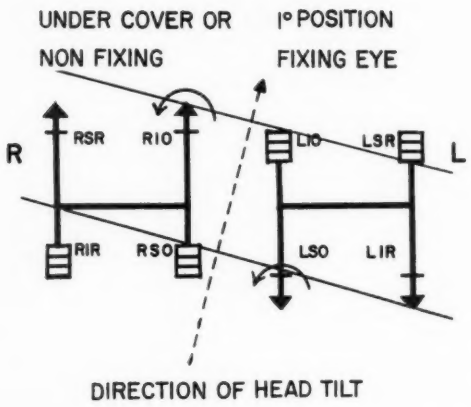


FIG. 6



vertical axis when the eye is in the slightly abducted position.[14] Upon looking up the inferior oblique is obviously posterior to the vertical axis. This should increase the abducting action of the inferior oblique on upward gaze.

Upon looking down the inferior oblique is anterior to the vertical axis and thereby increases its adducting activity.

The superior oblique would appear to be an adductor in both upward and downward gaze.

It is unwise to consider the vertically acting muscles as acting only in two planes—vertical and horizontal. One must remember that a large percentage of these cases have definite cyclorotatory activity which is notable on screening. It is our contention that the clinical picture evolves from a demand for cyclorotatory parallelism. Since the primary cyclorotators are the oblique muscles, the basic defect would appear to be in the balance between the superior and inferior

FIG. 7

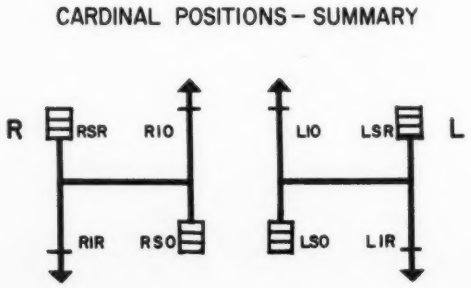
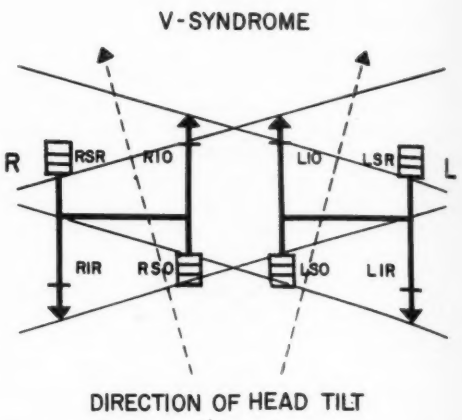


FIG. 8



oblique of the same eye. The reactivity of the muscles would appear adequate. One commonly notes a cyclorotation in the field of action of the supposedly defective muscle on forced fixation.

In our series, including both syndromes, a significant number have rotatory nystagmus which is markedly increased on monocular fixation.

A patient with a typical V or X syndrome will have the following findings on enforced alternate screening:

The nonfixing eye will usually be up and in or up and out.

In a chronically one-eyed fixing individual it is imperative that the alternate hypertropia be determined before surgical intervention is attempted.

Treatment.

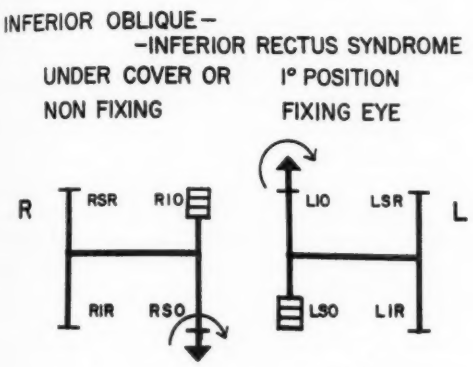
1. Primarily surgical.

2. The treatment of choice should be the inferior obliques if the horizontal deviation is less than the vertical. The standard procedure is myomectomy of the inferior oblique.

3. If there is a large vertical and horizontal deviation both the inferior obliques and the medial or lateral recti should be operated. The surgery should be symmetrical and in one stage.

4. If the vertical measures less than 5 diopters in the primary or cardinal position for distance or near, only the horizontal muscles are operated. (Our experience with movement of the horizontal or vertical rectus

FIG. 9



insertions is insufficient to include in this series.)

5. If a significant double hyper is not picked up on repetitive testing, then only the offending oblique is operated.

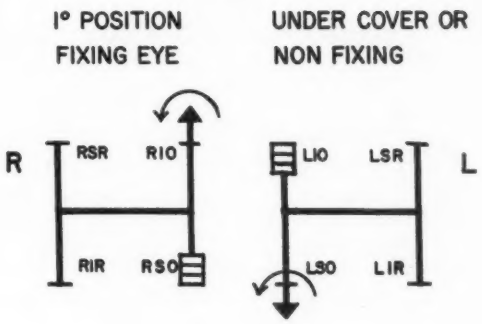
A Syndrome

The hypothetical development of the A syndrome could be as follows:

1. (Fig. 9) Left eye fixing, there is underaction of the *right inferior oblique* with associated overaction of the *right superior oblique*. When the eyes look up and left, there will be a relative overaction of the *left superior rectus* because of the underaction of the *right inferior oblique*. Looking down and left there will be a relative underaction of the *left inferior rectus* to the *right superior oblique*.

The overacting *right superior oblique* will cause incyclorotation of the right eye which

FIG. 11



is matched for cyclorotatory parallelism by excyclorotation of the left eye.

2. The result of this is seen in figure 10. In addition to the above there will be underaction of the *right superior rectus* up and right and overaction of the *right inferior rectus* down and right.

3. When the opposite eye is forced to fix, the exactly opposite picture will occur (Figs. 11 and 12).

4. The summary of cardinal positions (Fig. 13) brings us to the full-blown clinical picture (Fig. 14).

A patient with a typical *A* syndrome will have the following findings on enforced alternate screening:

The nonfixing eye will usually be down and in or down and out.

Treatment.

1. Primarily surgical.
2. If the vertical defect is greater than the

FIG. 10

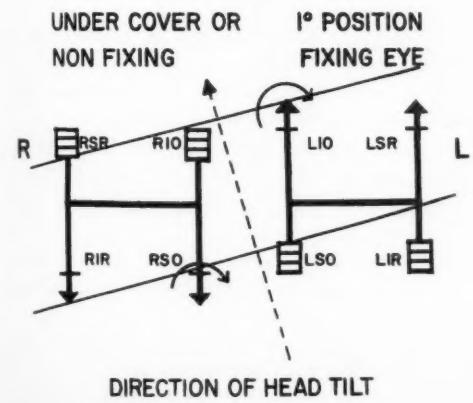


FIG. 12

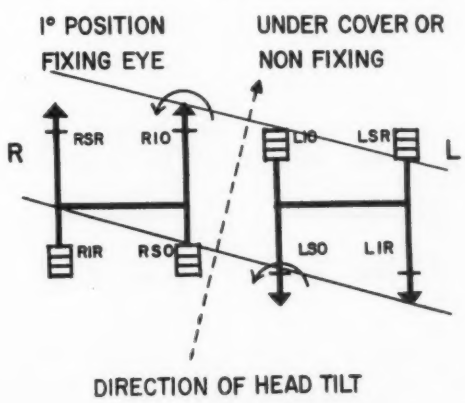
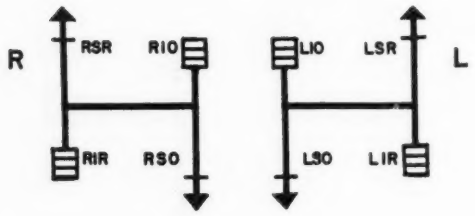


FIG. 13

CARDINAL POSITIONS – SUMMARY



horizontal, the superior obliques are tenotomized symmetrically.

3. When the vertical defect and horizontal defect are large, both horizontal and superior oblique muscles are operated at the same time. The procedure is repeated on the second eye.

4. When the vertical defect is less than 5 prism diopters in the primary position, for distance or near, symmetrical horizontal surgery is performed first.

Results

1. In this series of 150 operative cases, 12 have been drawn from the Receiving Hospital Muscle Clinic. (The Clinic has been in operation for only 2 years and adequate follow-up is not available.)

2. Since 1954 the inferior oblique myomectomy has been a standard operation. The superior oblique tendectomy has been utilized since 1958. No post-surgical paresis has been noted to date with either procedure (over 150 inferior oblique myomectomies and about 25 superior oblique tendectomies).

3. All of the cases have been evaluated and followed by trained orthoptic personnel. Orthoptic training is considered beneficial but is not a subject for this paper.

4. There are several cases of V esotropia in which correction of the accommodative factor effected reduction in the V component, leaving an alternate overaction of the inferior obliques and a horizontal tropia for distance, intermittent at near. To date symmetrical oblique surgery alone has placed these children in a full fusion situation. These cases will be presented at a later date.

5. Although upward and downward measurements are not available in all cases, there is evidence to show that the A or V component is markedly reduced to absent in those cases which have combined horizontal and oblique surgery done symmetrically.

6. *Total Number of Cases.*

Right and Left Superior Oblique—
Superior Rectus
with Esotropia = VET = 106
with Exotropia = VXT = 22

Right and Left Inferior Oblique—
Inferior Rectus
with Esotropia = AET = 8
with Exotropia = AXT = 15

Total Number of Cases 151

7. *Right and Left Superior Oblique–Superior Rectus = VET* (Table 1).

	*NI	†Cosmosis	‡Fusion
Recession			
Internal Recti	18	4	

15 of the NI cases had 1 or more further surgeries to cosmosis.

1 case had symmetrical IO myomectomies and resection of externi to fusion.

2 cases had symmetrical IO myomectomies and resection of externi to 1° fusion.

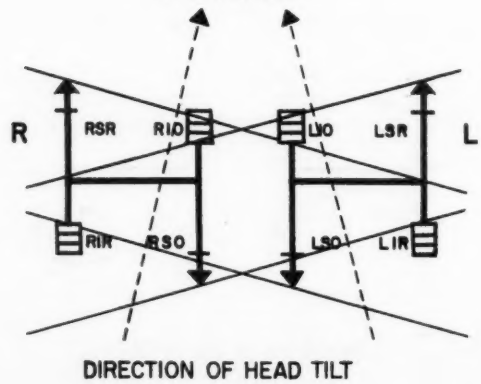
*—angular measurement essentially the same as before surgery.

†—cosmetically satisfactory. Often well within an angle of superimposition but no fusion attained.

‡—fusion—second or third degree. Able to work with stereopsis targets.

FIG. 14

A-SYNDROME



DIRECTION OF HEAD TILT

NI Cosmosis Fusion

TABLE 1

	Result	Age	Improvement Horizontal	Improvement Vertical	To Alt. H	Operation	Comments
1.	C	2	30△	10–25△			Very close
2.	C	3½	30△	0		Resection LLR Recession LMR	DH
3.	F	3	20△	5–10△		IO myomectomies, O. U.	Retarded
4.	C	4	20–25△	2–6△		MR recessions and IO's	Very close No V
5.	F	6	24–48△	0		MR recessions	Still has H
6.	C	7 mos.	100△	10△	To Alt. H	MR recessions LR resection and IO's RIO and RMR recession	
7.	F	5	40△	10△	To Alt. H	MR recession, O. U. LIO	2° Fusion
8.	C	15	20△	3△		MR recession, O. U. Tuck externi, O. U. Myomectomy IO's	
9.	F	13	50△	10 and 10△		MR recession and myomectomy IO's	E with amplitude
10.	F	7	4–6△	10△	To Alt. H	LIO myomectomy	
11.	C	10	10–20△	12△	To Alt. H	LIO myomectomy LR tuck and resection	
12.	C	7	35–55△	4–6△		IO myomectomies 2 operations MR recession and LLR tuck	Excellent
13.	F	6	50△	6–15△	To Alt. H	Recession RMR Myomectomy RIO Myomectomy LIO	2 operations, still V
14.	C	17 mos.	31–35△	8–10△		MR recession IO myomectomy	
15.	F	2	50△	6–10△		MR recession IO myomectomies	
16.	C	3	15△	18△	To Alt. H	Myomectomy LIO	
17.	C	2	50△	10–18△		Myomectomy IO's Recession LMR	Still ET No vertical
18.	C	13	20△	10△		LIO myomectomy then RIO myomectomy	
19.	C	10	4–25△	4–10△	To Alt. H	Recession RLR Tuck LLR Myomectomy LIO	
20. C	C	9 mos.	30–40△	6–10△		MR recession then IO's, then tucks Externi, O. U., then recession RIR	Marked improvement
21.	C	3	6–10△	4–18△	To Alt. H	Recession LMR Myomectomy LIO Myomectomy RIO Recession RLR	
22.	C	?	25△	0		MR recession	DH
23.	C	6 mos.	?	?		Myomectomy IO's Recession LMR	Optic atrophy Rotatory nystagmus
24.	NI	1½	NI	0		MR recession, O. U.	ET and DH
25.	C	2	30△	0		MR recession, O. U.	DH
26.	C	3	40△	8–20△		Myomectomy IO's Recession LMR	
27.	C	1½	40–50△	18△	To Alt. H	Recession MR, O. U. Myomectomy LIO LR resection and IO myomectomies Recession LSR Recession LMR	Monocular fixation Rotatory nystagmus
28.	C	3	2–4△	9△		LMR recession Recession LR, O. U.	DH
29.	F	3	85△	10–20△		MR recession IO myomectomies, O. U.	Unstable fusion
30.	C	7	40–50△	2–4△		Recession LMR Myomectomy IO, O. U. RMR recession LLR tuck	
31.	C	7	8–12△	5–6△	To Alt. H	Recession LMR Myomectomy LIO	
32.	C	3	12–15△	0		Recession interni, O. U. Tuck externi, O. U.	To A, Hyper persists

TABLE 1 (continued)

	Result	Age	Improvement Horizontal	Improvement Vertical	To Alt. H	Operation	Comments
33.	F	4	35–40△	0		Recession MR, O. U. Resection LR, O. U.	Fusion in 1° position DH
34.	C	5	7–35△	7△	To Alt. H	MR recessions LIO myomectomy	Monocular fix. Nystagmus
35.	C	5	43–38△	5–7△	To Alt. H	MR recessions Myomectomy LIO	
36.	C	12	20△	0		Lateral rectus tucks IO myomectomy, O. U.	Previous muscle surgery
37.	C	6	27–28△	10–12△		Myomectomy IO's, O. U. tuck RLR	Previous muscle surgery
38.	F	1	25△	5–10△		MR recessions, O. U. IO myomectomy, O. U.	Fusing-slight DH Fix. nystagmus
39.	NI	1	–	5△	To Alt. H	Recession LMR Myomectomy LIO	Constant nystagmus
40.	F	4	35–40△	0		Recessions MR, O. U. Resection LR, O. U.	Fusion in 1° position with DH
41.	C	2½	18–31△	8–10△	To Alt. H	MR recessions, O. U. RIO myomectomy	
42.	F	7		8–10△		IO myomectomy, O. U.	DH persists
43.	C	6 mos.	34△	5–10△		MR recession, O. U. RIO myomectomy Tuck externi, O. U., LIO myomectomy	
44.	C	2½	22△	14△	To Alt. H	MR recession, O. U. LIO myomectomy	Monocular nystagmus VET gone
45.	F	6	18–38△	13–16△	To Alt. H	MR recession, O.U. LIO myomectomy RIO myomectomy	2° fusion
46.	C	1½	30–40△	18△		MR recession, O. U. IO myomectomy, O. U.	
47.	C	1½	0	24△		RIO myomectomy	
48.	C	1½	20△	0		MR recession, O. U.	Alternate ET with DH
49.	C	1	15–30△	0	To Alt. H	MR recession, O. U. Myomectomy LIO	
50.	C	3	8△	10△	To Alt. H	Recession LMR Myomectomy LIO Resection RLR Myomectomy RIO	
51.	C	1	20–30△	5–10△		MR recession, O. U. Tuck LR, O. U. Myomectomies IO's O. U.	
52.	C	1	20–30△	5–10△		MR recession, O. U. RIO recession RLR tuck LIO recession LMR recession LMR advancement and resection	
53.	C	6	0	4△	To Alt. H	LIO myomectomy	
54.	C	13	6△	6–8△	To Alt. H	RLR resection RIO myomectomy	
55.	F	8	50△	20△		Myomectomy IO's MR recession, O. U.	
56.	C	15	8△	3–5△	To Alt. H	Recession RMR Resection LLR Myomectomy RIO	2 previous surgeries
57.	C	5	40–30△	4–8△		Recession MR, O. U. Myomectomy IO's, O. U.	Excellent position
58.	C	1	10–15△	5△	To Alt. H	Recession RMR Recession RIO Myomectomy LIO Recession LMR	
59.	C	4	40–45△	5–10△		MR recession Myomectomy IO's, O. U. Recession externi	Excellent position
60.	C	8	15–28△	10△	To Alt. H	LMR recession Myomectomy RIO	Excellent position
61.	C	1	15–20△	10–14△		MR recession, O. U. Recession IO's, O. U. Tuck RSO Myomectomy RIO	Excellent position
62.	C	1½	15–20△	5–10△		Recession LMR Tuck LLR IO myomectomy, O. U. Tuck RLR	

TABLE 1 (continued)

	Result	Age	Improvement Horizontal	Improvement Vertical	To Alt. H	Operation	Comments
63.	C	2	0	18△	To Alt. H	LMR recession LLR tuck LIO myomectomy	
64.	C	5	8–14△	3–7△	To Alt. H	Myomectomy RIO	
65.	F	2	48△	N.M.		Bilateral MR Bilateral IO's	
66.	C	14 mos.	25△	8–10△		Bilateral MR recession RIO recession	Excellent position
67.	F	3	15△	N.M.		LMR recession IO myomectomies, O. U.	
68.	F	7	24–35△	3–5△	To Alt. H	MR recession, O. U. RIO myomectomy RLR tuck	
69.	C	12	18–22△	9△	To Alt. H	LIO myomectomy Tuck externi	Previous surgery
70.	C	2½	21△	3–5△	To Alt. H	Myomectomy LIO Recession LMR	
71.	F	15	6–16△	3–5△		Recession RMR Myomectomy RIO	Nystagmus
72.	C	3	40△	8–20△		Recession LMR Myomectomy IO's, O. U.	
73.	C	1	15△	16△		Recession RLR Myomectomy RIO	
74.	F	1½	30△	15△		Resection externi, O. U. Myomectomy IO's, O. U.	
75.	C	1	30–50△	15△		Bilateral medial recession Myomectomy IO's, O. U.	Marked improvement
76.	C	3	13–17△	6△		LIO myomectomy	
77.	C	16 mos.	12–22△	6–12△		Recession IO's, O. U. Bilateral medial recession tuck RSO Tuck externi, O. U. RIO myomectomy	
78.	F	17 mos.	50△	11△		Bilateral recession interni Resection externi Myomectomy IO's, O. U.	
79.	F	3	40–50△	20△		Myomectomy IO's, O. U. Bilateral MR recession	Nystagmus
80.	C	1	30△	15△		MR recession, O. U. Resection externi, O. U. Myomectomy IO's, O. U.	
81.	C	1	75△	10–15△		Recession LMR Tuck LLR Tuck RLR Recession RMR Myomectomy IO's, O. U. Recession LMR	
82.	F	1½	22△	5△	To Alt. H	Myomectomy LIO Recession LMR Myomectomy RIO	
83.	C	1	20–30△	11△	To Alt. H	LIO myomectomy Recession RMR	
84.	C	1	30–10△	20△		Bilateral medial recession Tucks externi Myomectomy IO's	
85.	C	6	8–15△	5△		Myomectomy LIO	Excellent position
86.	F	1½	58△	10–15△		Recession interni Myomectomy IO's, O. U. Tuck RLR	Nystagmus
87.	C	2½	18△	4–10△	To Alt. H	Medial recession, O. U. LIO myomectomy	Nystagmus Excellent position
88.	C	9	7–15△	6△		RIO myomectomy	Previous surgery Rotatory nystagmus
89.	C	5	60△	35△		Recession RMR Myomectomy RIO Tuck LSO Recession LMR	
90.	C	2½	18△	7–20△	To Alt. H	Bilateral medial recession RIO recession LIO myomectomy	
91.	C	13	6△	6△	To Alt. H	Recession RLR Myomectomy RIO	Previous surgery
92.	C	14	20–36△	10–13△		Bilateral medial recession IO myomectomy, O. U.	Marked improvement

TABLE 1 (continued)

	Result	Age	Improvement Horizontal	Improvement Vertical	To Alt. H	Operation	Comments
93.	C	14	4–6△	3–5△	To Alt. H	RIO myomectomy RMR recession	
94.	C	1	60△	10–15△		5 operations	
95.	F	1½	16–26△	3–10△		Recession IO's, O. U. Recession LMR LSO tuck	
96.	F	6	18–21△	5–10△		IO recession, O. U.	Previous surgery Monocular nystagmus
97.	C	4	30–35△	4–9△		Bilateral medial recession Bilateral IO Myomectomies	
98.	F	4	2–4△	3–5△		IO myomectomies, O. U.	
99.	C		25△	7△	To Alt. H	Recession LMR Tuck LLR Myomectomy RIO Recession RMR Tuck LLR	Nystagmus
100.	C	16 mos.	50△	6△	To Alt. H	RIO recession RMR recession Myomectomy LIO LMR recession	
101.	C	3½	0	6–12△	To Alt.	Recession RIO Tuck RLR Recession LIO Tuck LLR	
102.	C	5	55△	5△		Recession RMR Tuck RLR Recession LMR Myomectomy LIO Recession LLR	Monocular nystagmus
103.	C	1	60△	20△	To Alt. H	MR recession, O. U. Recession RIO	
104.	C	2	30△	12△	To Alt. H	Recession MR, O. U. Recession LIO Myomectomy	
105.	NI	1	5–10△	0		Bilateral medial recession Bilateral IO's Bilateral tucks externi	Poor fixation one eye
106.	C	6	30△	10△	To Alt. H	Bilateral medial recession Recession LIO	
Average		4½	28.7△	9.3△			

C—Cosmosis
F—Fusion
NI—No Improvement

Symmetrical Horizontal, O.U. and Myomectomy. 1 oblique	1	14	1
(Some of the vertical surgeries followed previous horizontal surgery)			
Myomectomy of 1 inferior oblique	1	5	1
Myomectomy of 2 inferior obliques and 1 horizontal rectus	0	7	0
Myomectomy of 1 inferior oblique and 1 horizontal rectus	2	17	3
Symmetrical Horizontal, O.U. and Myomectomy IO's	0	10	8
Myomectomy of 2 inferior obliques	1	3	4

(The NI case was able to fuse after horizontal surgery.)

8. *Superior Oblique—Superior Rectus with Exotropia = VXT* (Table 2).

	NI	Cosmosis	Fusion
Recession LR, OU, Myomectomy LIO	0	0	2
Recession LR, OU, Myomectomy OU (* I prev. op.)	0	3*	0
Horizontal surgery only (* double hyper remains)	0	1*	0
MR tuck or resection and LR recession IO Myomectomy	0	2	0
Recession LR (1) and Myomectomy IO (* to opposite H)	1*	1	6*

TABLE 2

VXT

Result	*Age First Operation*	*Improvement Horizontal*	*Improvement Vertical*	*To Alt. H*	*Operation*
F	10	25△	15△		Recession LR and LIO
C	15	15–20△	5 or		LR and IO's
C	48	70	0△		2 sets horizontal surgery
C	—	18–30△	10△	Alt. H	Tuck MR Recession LR Myomectomy LIO
NI	7	0	15△		Recession LLR Myomectomy LIO
F	3	3–5△	25△	Alt. H	2 operations Recession RLR and RIO Recession LLR and LIO
F	5	20–28△	5△	Alt. H	Recession RLR, RIO Recession LR
F	11	10–35△	5△		2 operations Tuck RMR Myomectomy RIO
F	13	20–20△	12△	Alt. H	Recession LLR and LIO
C	56	10–20△	13–18△		Tendectomy RLR Myomectomy RIO
C	7	7–10△	5 and 5△	Alt. H	Recession externi O. U. Myomectomy RIO Myomectomy LIO
F	11	10△	14△		Recession RLR Myomectomy RIO
F	6	10–12△	6–12△	Alt. H	Recession RLR Myomectomy RIO
C	3½	15–30△	4–5△		Recession RLR Myomectomy IO's 1 previous surgery
F	39	7△	10△		Myomectomy LIO
C	27	21–16△	9–12△		Recession and advancement RMR Myomectomy RIO Recession RLR
F	7	0–5△	12–20△	Alt. H	2 procedures Myomectomy LIO Recession RIR
F	4½	21–37△	12–14△		Recession LR, O. U. Myomectomy LIO
NI	11	–7–15△	8–12△	Alt. H	Recession RLR Recession RIR
F	21	5–7△	4△		Tuck RSO
F	6	9△	5△		Recession RLR Recession RIO
C	13	56△	5–10△		Recession and Reattachment LMR Recession externi, O. U. Myomectomy RIO Previous surgery
Average	15.4	18.9△	9.8△		

Myomectomy 1 oblique	0	0	3
Recession RLR and Recession IR	1	0	0
Tuck RSO	0	0	1
Resection MR and 1 oblique	0	1	0
	2	8	12

9. *Right and Left Inferior Oblique—Inferior Rectus = AET* (Table 3).

	NI	Cosmosis	Fusion
Recession MR, OU and Tendectomy SO's		1 (adult)	
Recession RSR Tuck RLR			1
Recession LMR Recession LSO	1		
Recession LSO and Tendectomy LSO			1
Recession MR, Tuck LR Myomectomy opp. IO			2
MR recession and SO Tendectomy			1
Transplant SO to SR	1		
	2	6	0

TABLE 3

AET

Result		*Improvement Horizontal*	*Improvement Vertical*	*To Alt. H*	*Operation*
C	20's	40–50△	12–20△		Recession MR, O. U. and SO Tendectomy, O. U.
C	6	20△	10△		Recession RSR Tuck LR
NI	8	–	–		Recession LSO Recession LMR
C	?	50△	10△		1. Tuck LR, O. U. Recession MR., O. U. 2. Recession SO and myomectomy SO
C	2½	27△	12△	To Alt. H	Recession RMR then myomectomy LIO and tuck LLR
C	6	100△	0		1. Bimedial recession 2. LSO tendectomy
C	6	40△	13△	To Alt. H	Bilateral MR and RIO
NI	6	–	–		Transplant SO
Average	8½	45.4△	10.1△		

10. *Right and Left Inferior Oblique—Inferior Rectus = AXT* (Table 4).

	NI	Cosmosis	Fusion
LR recession SO Tendectomy 2 stage			1
LR recession	1		1
SO Tendectomy	3		
LR recession and SO Tendectomy	1		
Recession ILR Myomectomy opposite oblique	1		
Myomectomy opposite oblique	1	1	1
Resection IMR Recession LR		1	
Recession Superior Rectus			2
Myomectomy both Inferior Obliques	1		
15 cases	2	8	5

11. Total cases with horizontal surgery and 1 oblique 52

TABLE 4

AXT

Result	*Age First Operation*	*Reduction in Horizontal*	*Reduction in Vertical*	*Follow-up*	*Operation*
F	6	35△	12△	6 months	LR Recession followed by separate SO Tendectomy
C	15	20–40△	0	1 year	LR only
C	4	18△	20–35△	4 months	SO only
C	10	18△	6–8△	Not known	SO only
C	14	20△	10△	3 months	SO and LR, O. U.
C	35	35△	5–10△	3 months	SO and LR, O. U.
*NI	7	10△	LH7△ RHO△	1 year	Recession LLR Myomectomy LIO
C	10	2–10△	Same	1 year	Recession Externi, O. U.
F	50+	20△	14△	2 years	Myomectomy IO's
C	10	8△	4△ No longer A	2 years	Myomectomy IO's
F	7	30–40△	4–6△	–4 years	Recession LMR Recession LLR Myomectomy RIO
F	7	0	4–6△	–2 years	Recession RSR
F	10	12△	4△	–2 years	Recession RSR
NI	10	–	–	–4 years	Myomectomy IO's
Average	13.9	19△	8△		

*Slight

Total cases with horizontal surgery and 1 oblique going to opposite Hyper. 40

12. Nystagmus with Alternating Hypertropia

I.	13 cases	/ 106
II.	2 cases	/ 22
III.	1 case	/ 8
IV.	1 case	/ 15
	17 cases	/ 151

13. *Effect of V or A Measurements.*

Those cases who had surgical intervention to the oblique muscles (Inferior or Superior Oblique) had measurable reduction in the difference between upward and downward position even when the result was cosmosis and not fusion.

Conclusions

I. (1) Superior Oblique—Superior Rectus ET = VET. An alternating esotropia with overaction of both inferior obliques would appear to get the best surgical result with operation on the inferior obliques and the horizontal muscles (symmetrical). (2) Superior Oblique—Superior Rectus XT = VXT. An alternating exotropia with overaction of both inferior obliques would appear to get the best surgical result with operation on both inferior obliques and both externi (recession). (3) Inferior Oblique—Inferior Rectus ET = AET. The best results to date evolve from surgical intervention on the superior obliques and the horizontal muscles. (4) Inferior Oblique—Inferior Rectus XT = AXT. The best results to date evolve from surgical intervention on the superior obliques and the horizontal muscles.

II. Adequate and repetitive examination including cardinal positions is essential to diagnosis. The vertical defect must be determined with either eye fixing.

III. Once the diagnosis is established, symmetrical surgical intervention to both the horizontal and vertical muscles is indicated with a horizontal tropia having a notable alternating hypertropia. If the vertical component is more notable than the horizontal, symmetrical vertical surgery (before horizontal surgery) is indicated.

IV. There is a real incidence of hypertropia to the opposite side when only one vertical muscle is operated.

V. Horizontal surgery in the presence of a measurable vertical component will not result in a satisfactory result and will usually require further intervention; usually to both horizontal and vertically acting muscles.

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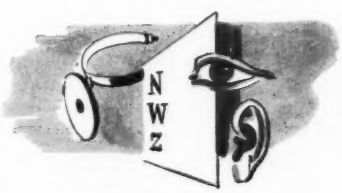

The Carcinoid Syndrome: Its Diagnosis and Management*

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This rare disease is being recognized more frequently since an increasing number of clinical reports are appearing in the literature. As yet no definitive means has been found of controlling the metabolic abnormality.

Nature of the Syndrome

THE TERM CARCINOID is applied to a low-grade carcinoma originating in the argentaffin cells of the digestive tract or elsewhere in the human system where these cells exist. It is a tumor formed from the chromargentaffin cells, and though usually found in the enteric canal (i.e., the appendix, the ileum, the jejunum, the rectum, the colon, the stomach, and the gallbladder), it has occurred in the bronchial tree and in the testicles. The vast majority, from 58 to 90%, apparently has occurred in the appendix.[1]

This neoplastic lesion has been recognized for many years, but originally was considered to be benign. Not until 7 years ago was it realized that about 10% of carcinoids may function as endocrine tumors in that they secrete serotonin. Since then, these tumors have been known as *functioning carcinoids* in the United States,[2] and Broders[3] has used the classification, *functioning adenocarcinoma, carcinoid type*. In the Scandinavian and other foreign countries wherever they have been described, they have been known as *metastasizing argentaffin carcinomas*.[4] When a carcinoid functions as an endocrine tumor and secretes serotonin, the vessels of the skin, the smooth muscles of the gastrointestinal tract and of the bronchi, and the valves of the heart are affected. In some instances disturbed function of the brain has been suspected, and this possibility is being investigated. Ordinarily, an endocrine tumor acts through its hormones, causing overstimulation of normal physiologic processes (i.e., the production of hypoglycemia by an islet cell adenoma of the pancreas). If the carcinoid functions, the syndrome developed and the clinical picture produced are entirely pathologic.

Diagnosis

The cardinal symptoms of a functioning carcinoid include the flushing phenomenon of the skin, diarrhea, episodes of asthma, enlargement of the liver, dependent edema, auscultatory findings typical of pulmonic stenosis or tricuspid insufficiency, and a history compatible with previous episodes of intermittent, incomplete obstruction of the small bowel.

The peculiar flushing of the skin has been mentioned by all who have described this syndrome. When present, it is perhaps the most outstanding physical finding, and remarkably descriptive terms have been applied to it. For instance, one patient's husband said of his wife's condition, "She gets red as a lobster," and "She looked red, as if she were on fire." She described the flushing as, "My skin felt as if it were burning." Associated with the flush, an intense feeling of warmth and, at times, rather severe perspiration occurs. The head, neck, thorax and arms usually are involved; although, sometimes, the flushing covers the entire body. The skin appears florid; the scleras are injected; red, blotchy, geographical areas without elevated edges may appear. These areas tend to fade from the center to the periphery. The central portion becomes dusky, then cyanotic, before the discoloration disappears and leaves the skin normally white. At first, these areas might simulate giant hives, but they are not elevated above the surface of the skin. The attacks may be precipitated by hot drinks, eating, defecation, anger, anxiety, and by massage of the abdomen — especially over the liver.

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Women who have these spells stress the difference between them and the hot flushes of the climacterium. It has been thought that the syndrome does not manifest itself except in the presence of metastatic liver disease.

The signs and symptoms of a functioning carcinoid are due to the increased production of a pharmacologically active substance, 5-hydroxytryptamine or serotonin, by the malignant cells; and the clinical diagnosis can be confirmed by detecting abnormal amounts of 5-hydroxy-3-indolacetic acid in the urine. This acid gives the urine a characteristic purple color. On some occasions the carcinoid syndrome can be diagnosed without detecting a tumor before abdominal exploration.

Normally, a 24 hour urine specimen will contain about 2 to 9 mg. of 5-hydroxy-3-indolacetic acid, and higher values are considered abnormal. Because ingestion of bananas has led to an increased excretion of 5-hydroxy-3-indolacetic acid in monkeys and also in children, bananas should not be eaten before the test is made. Tryptophan apparently acts as a loading agent, hence, administration of tryptophan will increase the secretion of serotonin. If a functioning carcinoid is present, the majority of the administered tryptophan will be delivered over the serotonin pathway to form serotonin, with eventual degradation to 5-hydroxy-3-indolacetic acid; however, the increase often is not dramatic.[2]

When serotonin is injected intradermally into one arm and histamine phosphate into the other, the serotonin reacts and produces marked erythema on the flexor surface of the forearm and cyanotic fingertips. Sometimes, the erythema covers a large area of the body. A similar reaction is not observed in the region injected with histamine.[4,5] As compared to the reaction in normal persons, a patient with a malignant carcinoid tumor will hyper-react when serotonin is administered intradermally. Injections of histamine or diphenhydramine HCl (Benadryl) do not affect the flushing.

Associated Lesions. A rather high incidence of gastric and duodenal ulcers has been associated with functioning carcinoid tumors. This is one of the reasons why histamine or histamine-like substances have been considered important in the production of this syndrome. Also, some relationship between these tumors and arthritic changes, usually found in the joints of the fingers, has been suggested.[4] In the literature, dermatomyositis has been reported in persons who have carcinoid tumors; or vice versa, patients who have dermatomyositis may also have carcinoid tumors.[6] Asthmatic attacks occur frequently in these patients.[7] Valvular lesions of the heart are quite common,[8,9] and MacDonald[10] reported that 34 of 57 patients had isolated nonrheumatic lesions of the valves of the right side of the heart or combined lesions in the right and in the left side. Edema of the face, feet, and ankles is not unusual.

Management

Management of the patient with a carcinoid tumor presents many difficulties.[11] Surgical removal of as much of the malignant tissue as is possible is indicated. This should be done, especially if large metastatic masses involve mesenteric glands, in an effort to remove enough bulk of the tumor to reduce formation of serotonin and thereby to lessen symptoms. Caution during surgical intervention must be advocated. Stacey[7] reported 2 instances in which attacks, ultimately leading to death of the patients, developed at early stages of the operations before any tumor tissue was manipulated. Similar difficulties have been encountered by Waugh.[12]

A serotonin antagonist such as 1-methyl-d-lysergic acid butanolamide tartrate (UML-491) has been given by slow infusion with rather equivocal results; however, at times, the flushing is attenuated. Giving the drug by mouth in increasing doses of 2 to 12 mg. a day affects the flushing only minimally. Much hope has been held that some of the reported antagonists of serotonin would be of value.[4]

As reported previously, our experiences with chlorpromazine have been promising.[2] According to others, brominated lysergic acid diethylamide has been tried, but Bean and Funk[13] did not note changes in signs or symptoms or diminution of the excretion of 5-hydroxy-3-indolacetic acid after its use. They also reported a trial of 1-benzyl, 2-methyl, 5-methoxytryptamine hydrochloride in doses of 25 mg., three times a day for periods of two weeks, without clinical effect or significant changes in the excretion of 5-hydroxy-3-indolacetic acid. We have used as much as 200 mg. of chlorpromazine a day and also hydroxyzine without significant improvement in some of our patients.

Smith and co-workers[5] stated that brominated lysergic acid did not cause significant clinical response, although one patient excreted less 5-hydroxy-3-indolacetic acid. They also noted that reserpine provoked an overall increase in flushing and frequency of bowel movements. A marked increase in the excretion of 5-hydroxy-3-indolacetic acid was followed by a marked decrease, suggesting a period of relative depletion of this substance in the tissues. These authors proposed that this might be useful as a provocative test to detect nonsecreting tumors.

Symptomatic measures may be helpful in attempts to control the diarrhea. The tranquilizing effect of chlorpromazine may have some value. Stacey[7] has stated that since excitement and norepinephrine may precipitate asthmatic attacks in these patients, the use of this drug in the treatment of bronchospasm may be inadvisable. If large amounts of histamine are being excreted in the urine, administration of one of the antihistaminic agents may be of value.

Roentgen and radioisotope therapy have been tried in an effort to destroy metastatic tissue and to reduce amounts of circulating serotonin. Two of our patients received extensive roentgen therapy without obvious help. Stacey reported on 2 patients who received roentgen therapy without benefit and with actual deterioration; however, he stated that 2 additional patients received temporary amelioration after administration of radioactive gold.

Sjoerdsma and his associates[14] have reported that an inhibitor of aromatic amino acid decarboxylation, a-methyl-3, 4-dihydroxyphenylalanine (a-methyl-dopa) was administered to 2 patients with carcinoid tumors to determine whether the decarboxylation of 5-hydroxytryptophan (5-HTP) to serotonin might be inhibited. The most conclusive evidence that this was accomplished was the accumulation of the serotonin precursor, as indicated by a marked increase in the urinary excretion of 5-HTP. A 60 to 70% decrease in excretion of serotonin metabolite, 5-hydroxyindolacetic acid, also was indicative of effective inhibition of serotonin formation.

Summary

The carcinoid syndrome is being recognized more frequently as knowledge of the clinical features and of confirmatory laboratory procedures is being more widely disseminated. The carcinoid secretes serotonin and functions as an endocrine tumor.

To make a diagnosis of the carcinoid syndrome, all of the clinical features need not be present simultaneously. Demonstration of abnormal amounts of 5-hydroxy-3-indolacetic acid in the urine confirms the diagnosis. The amount of this substance in the urine may vary from time to time, and more than one determination may be necessary. Postoperative urinary determinations are of value in anticipating development of metastasis.

The treatment of choice is surgical removal of all or of as much of the tumor tissue as is possible to reduce the secretion of serotonin. Irradiation therapy is of doubtful value. To date, the serotonin antagonists have not been of as great aid in medical management as had been hoped. Symptomatic measures are indicated for relief of diarrhea, pain, and asthma.

The primary site of the lesion is usually the gastrointestinal tract, frequently the ileum; however, in some persons, the primary lesion seems to have been a bronchial adenoma of the carcinoid type.

Functioning carcinoids may exist without the clinical manifestations of the syndrome. In some patients, large amounts of serotonin may be present in tumor tissue, and high urinary values for 5-hydroxy-3-indolacetic acid are found although clinical evidence of the syndrome is absent.

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Discussion (Abstract)

Dr. John T. Sessions, Jr., Chapel Hill, N. C. First, I should like to compliment Dr. Bargen on his vivid description of the carcinoid syndrome and to thank him for having shown a film illustrating so colorfully the peculiar flushing of the skin seen in this rare disorder. The importance of this syndrome far exceeds its frequency since studies of serotonin, the hormone responsible for the disturbed physiology which has been described, has led to increased understanding of such common symptoms as emotional disturbances, altered bowel motility, and flushing of the skin. Today, I wish to point out theoretical and clinical evidence favoring a relationship between serotonin and some symptoms of a frequently encountered clinical disorder, hyperthyroidism.

The hormone serotonin (5-hydroxytryptamine, 5HT) when secreted by argentaffin cells of the small bowel normally passes by the portal vein to the liver where an enzyme, monamine oxidase, converts it to biologically inactive 5-hydroxy-3-indolacetic acid (5HIAA). Dr. Bargen has properly emphasized that even in the presence of large secreting carcinoid tumors, systemic effects of 5HT have been reported to occur only when the hormone bypasses the liver by hepatic metastases or extension to an area where venous drainage is not into the portal system. One might suspect, however, that drugs or diseases inhibiting hepatic monamine oxidase activity might allow systemic effects of 5HT to occur in the absence of a large metastasizing argentaffinoma. In fact, the monamine oxidase inhibitor iproniazid (Marsilid) has been reported to increase sensitivity of experimental animals to 5HT and in a patient with the carcinoid syndrome has increased symptoms while decreasing urinary 5HIAA. We have been interested, therefore, in the possibility that a disease associated with decreased monamine oxidase activity might allow normal or slightly increased amounts of 5HT to have systemic effects. Hyperthyroidism is such a disease.

A patient admitted because of urticaria, flushing of the skin, slight dyspnea, and diarrhea was found to have hyperthyroidism and the symptoms were explained on the basis of this disease. An attempt to increase her weight by feeding a high-fat diet provoked an exacerbation of symptoms in a manner similar to that described in the carcinoid syndrome by Bleehan (Lancet 269:1362, 1955). Urinary 5HIAA concentrations were normal, but we found the carcinoid syndrome could not be excluded at that time because the patient was receiving methimazole (Tapazole) and Lugol's solution, both of which interfere with color development in the clinical procedure usually used in testing for urinary 5HIAA. It might be added that chlorpromazine, promethazine HCl (Phenergan) and promazine HCl (Sparine) have also been reported to have a similar effect and might give one the false impression that in a patient with the carcinoid syndrome they were interfering with serotonin production or degradation.

Hyperthyroidism shares with the carcinoid syndrome an exquisite sensitivity to epinephrine and, as Dr. Bargen has pointed out, this drug should not be used in treating such patients who suffer from asthma or other allergic manifestations. Since monamine oxidase is important in the inactivation of epinephrine it is not surprising that in the carcinoid syndrome and hyperthyroidism effects of epinephrine are exaggerated.

Now for questions to enlarge on Dr. Bargen's presentation.

1. Are there clinical situations or disorders other than the excessive eating of bananas that might give an apparent increase in urinary 5HIAA and therefore require differentiation from the carcinoid syndrome?

2. Do you have experience in the use of isonicotinic acid hydrazide and alpha-methyl-dopa in the treatment of the carcinoid syndrome?

3. Since tryptophane is important in the synthesis of niacin and since in the carcinoid syndrome ingested tryptophane is shifted into the production of serotonin, did any of your patients show evidences of pellagra?

Thank you for the opportunity for discussing this excellent and interesting paper.

Dr. Bargen (Closing). In answer to the questions I will say that I am not familiar with any clinical situations or disorders which would give an apparent increase in urinary 5HIAA other than those mentioned. I have no experience in the use of isonicotinic acid hydrazide or alpha-methyl-dopa in the treatment of the carcinoid syndrome. None of our patients have shown any evidence of pellagra. Dr. Sessions' suggestions and additions to my paper are much appreciated.

The Day Hospital*

RONALD W. McNICHOL, M.D., and ARTHUR L. SEALE, M.D.,†
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Much experimentation in the management of the psychotic persons is in progress. This discussion concerns itself with the objectives of psychotherapy during the daytime, the patient returning home to spend the night.

THE TREATMENT OF MENTAL ILLNESS and the concept of the role of the mental hospital have changed radically within the past decade. One of the most significant developments has been the realization that in many cases, and perhaps in most, hospitalization is not only costly and unnecessary but is an actual deterrent to recovery and rehabilitation. From this new thinking have come many experiments, suggestions and ideas: the Mental Health Clinic for outpatient service, the Diagnostic Center, the Day Hospital, Night Hospital, Well-being Clinic, and others. While there are many similarities, there are also considerable differences among them.

The present paper is concerned with two Mental Health Treatment Centers organized within the Mental Health Division of the Louisiana Department of Hospitals. These Centers include the Day Hospital as a part of their total function. They encompass a broader scope and a more flexible philosophy than does a Day Hospital alone, thereby providing a better approach to the total treatment of mental illness. Thus a Treatment Center may offer the service of a clinic, a Day or Night Hospital, or even additional facilities through which patients might be hospitalized for a brief time. It is more adaptable to the demands placed upon it and can therefore serve more effectively and more economically the needs of a larger group of patients drawn from a considerably greater geographical area.

A number of factors operating in the field of mental health have contributed to the development of a new approach to treatment and care of patients. Only in the thirties did we see the advent of insulin shock therapy and with it the first major breakthrough to many of the mentally ill. This was the spark that really lighted the fires of hope. It brought new enthusiasm and new ideas to the entire field. So far have these changes brought us, so greatly have they modified our thinking, that by 1958, Goshen[1] could state that we had reached a major turning point in the evolution of facilities for psychiatric care and confidently predict that "perhaps the most noteworthy and striking change developing in the years ahead will be the obsolescence of the standard public Mental Hospital." Solomon[2] also has called for new ways to meet the challenges saying, "A little pathwork on the old garment will not suffice; a few more nurses, a few more attendants, a little better pay scale, a little less overcrowding is not the answer."

Out of the renaissance of thought have come a number of solutions to particular problems. Cameron[3] introduced the term "Day Hospital" for what he termed "an experimental form of hospitalization for psychiatric patients" which was set up at the Allan Memorial Institute of Psychiatry in Montreal in 1946. He questioned the validity in a psychiatric unit of three concepts accepted in a general hospital: that a hospital is a place where the patient goes to bed; a hospital is a place where a patient stays until he is well, or as well as the doctor can make him, and that a hospital is a place where only the patient is treated.

On the contrary, he said, psychiatric patients do not need to stay in bed; they do not have to remain in the hospital until they are well, and indeed, often do not get well if we try to make them stay, and it is not only the patient but also his family unit and his general social setting which require to be treated. The Day Hospital which he set up provided the expression of these concepts.

More recently, Craft[4] has defined the Day Hospital as "one where full hospital treatment is given under medical supervision to pa-

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tients who return to their homes every night. It is suitable for those of the mentally ill who are well enough to travel and to spend the night with their families." Hunt[5] has described the Day Hospital in a more comprehensive setting as have Mandelbrote[6] and Boag.[7]

Interestingly enough, the Russians appear to have developed the same type of treatment somewhat earlier. Dzagharova,[8] in 1937, comprehensively described the Moscow Day Hospital which had opened in 1933 and his findings have been largely confirmed by the experiences in this country, in England and elsewhere. The development there, he said, "grew entirely out of life situations and even sharp necessity, for there was an acute need for beds in hospitals." One would suspect that this statement is true, although it would seem to contradict the thesis of his somewhat oratorical and politicalized introduction—that, while mental illness is raging rampant in the capitalistic countries, the very atmosphere of socialization in Russia is possessed of curative powers and, that since the Revolution, mental illness in Russia had sharply decreased!

The development of new treatment facilities in England has been more rapid, perhaps, than in any other country. The first Day Hospital was Marlborough, developed by Bierer[9] in 1948, independently of any parent mental hospital. Cosin[10] established the Day Hospital at the Oxford Geriatric Unit. Harris[11] described two Day Hospitals in London which followed closely the pattern outlined by Cameron: Maudsley, opened in 1953, and Bethlem, opened in 1956.

In North America, Moll[12,13] founded a Day Hospital in the Montreal General Hospital in 1950, and in 1954 established a Night Hospital there as well. Barnard and associates[14] described a Day Hospital opened at the Menninger Clinic in 1949 on the pattern established by Cameron, where foster homes are provided for patients who live out of town but who wish to take advantage of this type of treatment. A Day and Night Center were set up in the Yale Psychiatric Clinic in 1948-49. A Day Therapy Center was opened in Los Angeles by Hayman[15] in 1955. There are others and more are being planned.

Psychiatrists in other nations are moving in similar directions. Gillis[16] has described a Psychiatric Day Hospital in connection with Tara Hospital in Johannesburg, South Africa. The literature also includes a description of a Day Hospital in sparsely populated Newfoundland, run by Pottle.[17] Government subsidized transport and lodgings there ensure attendance of patients and all forms of treatment are given. In 1956, Lambo[18] adapted the concept to a Nigerian community using a Day Center with night foster homes.

In 1957 Hall[19] divided the 20 (now over 40) Day Hospitals in England and Wales into four general categories: those which are ancillary to an established mental hospital and share the regular hospital services, becoming the approximate equivalent of an additional ward; geriatric Day Hospitals, attached either to a hospital for chronic diseases or to the geriatric department of a general hospital, the independently operated Day Hospital (which may also include a Night Hospital using the same facilities) and, fourth, the center to which patients go at intervals during the week. The treatment centers in Louisiana may be considered to include in some measure characteristics of each of these categories.

To review briefly the history of the state hospital organization in Louisiana and provide the background against which we may interpret and evaluate the treatment centers which are now operating, we would note that Louisiana has rather consistently been among the pioneers in public health programs. East Louisiana State Hospital at Jackson was one of the first such state institutions in the country and was highly rated by Dorothea Dix when she visited there. Central Louisiana State Hospital was established in 1905 and a third hospital at Mandeville in 1950. A fourth was well along in the planning stage when a survey was made by a special committee headed by Dr. Daniel Blain, then Medical Director of the American Psychiatric Association. The committee recommended the establishment of the Treatment Center in Lafayette as an experiment to determine if the need could be met in this way, rather than by building a fourth State Mental Hospital. The Lafayette Center was opened in 1955 in an abandoned ambulance shelter adjoining the Lafayette Charity Hospital. Its success has eliminated the need for building a fourth mental hospital in the state.

Forest Glen Treatment Center, in Pineville, Louisiana, was opened in August 1959, in a

remodeled building which was part of a World War II government-housing project. It is located on grounds adjacent to those of Central Louisiana State Hospital. The building is a narrow, two-story structure, providing 10,000 square feet of floor space and its 200 by 25-foot dimensions made it less than ideal to arrange. This did not prove a serious problem, however, since by the extensive use of color, and opening up areas as much as possible, we have been able to get away from the "closed in" feeling which might seem almost inherent in so narrow a building.

On the first floor are the waiting rooms, offices, examining rooms, and a ward with 18 beds for the administration of electroshock and other physical therapies. Connected with this is a kitchen, where coffee and light meals may be prepared.

The upper floor is used almost entirely for group therapy and the occupational therapies including music, art, and bibliotherapy.

Throughout the building, comfortable, attractive surroundings and an air of informality have been emphasized. Color is used extravagantly in furniture and fixtures and on the walls, a device which we have found very effective here as well as in the main hospital. We might add that this color is used more as a "conversation piece" or an eye-stopper than with any consideration for the specific psychologic effects to be gained by a particular hue. It is amazing what a bit of purple, pink, blue and green can achieve!

The Forest Glen Treatment Center is administratively a section of Central Louisiana State Hospital which in turn is administered through the State Department of Hospitals. The full-time staff consists of a psychiatrist who is director of the center, a psychologist, two psychiatric nurses, two psychiatric social workers, one receptionist, two stenographers, three attendants, one occupational therapist and two custodial workers. Part-time staff includes a psychiatrist, general physician, music therapist and art therapist.

The philosophy of the treatment center is that most patients at all stages of mental illness can be treated in this type of voluntary setting. As far as hospital patients are concerned, it is completely separate. None of the hospital patients are treated there while they are inpatients, but are often referred for supportive therapy while they are on convalescent leave or after discharge. It is believed that while some patients may require daily care, particularly at the beginning of the treatment period, most patients should not be removed from their home environment to that degree, especially after they begin to show improvement. Just as a music teacher must allow students adequate time for practice between lessons, so, we believe, should treatment in many cases permit the patient to make his adjustment—or practice his lessons in living, if you will—at each level of his recovery. We believe this procedure may require treatment over a slightly longer period of time but that it will be more effective in the long run and its results more lasting.

Each center must serve a wide geographic area, bringing patients from considerable distances for treatment. The catchment area for Forest Glen during its initial 12 months of operation has encompassed a radius of more than 100 miles. The Lafayette center has, for 5 years, been serving patients located up to 75 miles distant.

Although it has been found in most cases that treatment on less than a daily basis can be quite satisfactory, there are undoubtedly some patients who could be managed more effectively, if it were possible to follow them more closely, over a period of a few days at the beginning of treatment. With this in mind, we are now planning to provide space where a patient and a member of his family can remain overnight if the distance to his home is so great as to make daily round trips unfeasible from both a physical and an economic standpoint. A well-being clinic has already been established on the basis described by MacLeod[20] and a Night Hospital will be established in the near future.

The aims of the center are to provide a place for the early diagnosis and treatment of mental illness; to provide outpatient facilities for mentally ill patients who would otherwise be forced to enter mental hospitals because of their inability to pay for private outpatient care and to provide a convenient follow-up for patients released from the mental hospitals. The lower age limit was somewhat arbitrarily set at 18, with the expectation that younger patients would be treated at the various Guidance Centers. This policy has not always been followed, one emergency case being an 8 year old boy.

Three hundred patients were referred to

Forest Glen in the first year of operation. Two thirds of these (200 cases) were considered to have moderate to severe psychiatric impairment which would have required commitment had our services not been available. The remainder, although less severely ill, nevertheless presented difficult management problems to the referring physicians.

Table 1 shows the diagnostic breakdown of the 300 cases.

Approximately 85% of the referrals were made by private physicians, the remainder by Central Louisiana State Hospital, the Department of Welfare, and other social agencies.

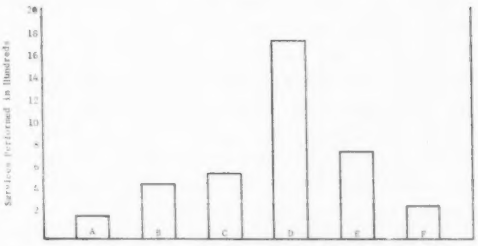
The private physicians, both specialists and generalists, have been most receptive to the service that the Treatment Center affords and there has been quite close contact with them. We believe it is essential to keep the referring physician informed as to the dispositions made on his patients. When a patient is discharged from the Treatment Center, he is advised to return to the care of the referring physician, and a covering letter is sent to the doctor at that time. The more fully the doctor is informed of our findings, the better prepared he will be to detect, evaluate, and cope with subsequent problems. The center now offers him a specialized treatment service, to which he may refer patients before they reach the stage at which commitment would be the only solution.

We referred 10 cases to Central State Hospital during the year, either immediately after initial examination or after they had failed

TABLE 1

I.	Chronic brain syndrome		13
II.	Acute brain syndrome		1
III.	Mental deficiency		10
IV.	Psychotic disorders		86
	a. Involutional	11	
	b. Psychotic depressive	5	
	c. Schizophrenia	70	
V.	Psychophysiologic reactions		3
VI.	Psychoneurotic reactions		144
	a. Anxiety	45	
	b. Dissociative	1	
	c. Conversion	2	
	d. Phobic	2	
	e. Obsessive-compulsive	4	
	f. Depressive	90	
VII.	Personality disorders		43
	Personality pattern	17	
	Personality trait	16	
	Sociopathic	10	
Total cases			300

TABLE 2



(A) Physical examinations. (B) Laboratory procedures. (C) Modified EST. (D) Progress interviews with patients, average duration 15 minutes. (E) Interviews with relatives. (F) Individual psychotherapy sessions, each of 30-45 minutes duration.

to show early response to treatment. Only two of the 10 cases required commitment, the others being admitted voluntarily. We have found that as our experience has increased we have been able to satisfactorily treat more severely ill patients than we had originally thought possible.

Forty-six patients were discharged during the year, most because of a favorable response to treatment, a few because referral was for evaluation only (e.g., court referrals). A few were terminated because of failure to keep appointments.

Services performed during the first year are shown in table 2. Additionally there were many psychologic testings, group and occupational therapy sessions and other services difficult to tabulate.

Operating costs (exclusive of capital costs) for the first year of operation totaled $51,695. Salaries accounted for $34,924, contractual services for $5,740 with materials and supplies totaling $11,031. The latter figure was divided about equally among: household, medical and general maintenance costs. The cost per patient day was slightly less than one dollar, based on the assumption that all patients were treated on a daily basis so long as they made regular visits to the Center. This is approximately 25% of the inpatient *per diem* rate at Central Louisiana State Hospital.

Contributions by patients based on a sliding fee scale totaled $1,700 for the 12 month period.

We believe that the Treatment Center, because of the accessibility of relatives, affords a unique setting in which to carry out research on family attitudes. This same accessibility of patients and relatives also affords

an opportunity to utilize mental health orientation in a meaningful way. An appropriate study is now nearing completion.

In summary we have described the operation of two mental health treatment centers in Louisiana with particular emphasis on one of them. These units include the day hospital as a part of their total function. Historical material has been presented along with pertinent facts and figures relative to the operation of a treatment center. We believe that the Day Hospital itself represents a major advance in the treatment of mental illness but that the use of these concepts, in a more comprehensive treatment setting is even more meaningful in the total treatment of the mentally ill.

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Discussion (Abstract)

Dr. Addison M. Duval, Jefferson City, Mo. The authors have given us some interesting food for thought in their paper entitled "The Day Hospital." Rather than discussing the "Day Hospital" alone, they have expanded their subject matter to include certain additional types of services for the mentally ill not furnished by the standard public mental hospital.

I cannot completely agree with the authors that "one of the most significant developments has been the realization that in many cases, and perhaps in most, hospitalization is not only costly and unnecessary, but is an actual deterrent to recovery and rehabilitation." I doubt seriously that the authors mean what they seem to say in this statement. Certainly, hospitalization is costly, but just as certainly, it is essential in certain cases. Their statement would seem to imply that hospitalization should *never* be instituted because it is *always* an actual deterrent to recovery and rehabilitation. I suspect what they mean to say is that mental hospitalization, like bed rest in community hospitals, can be overdone and in some instances may actually be a deterrent to recovery and rehabilitation. We know some of our large mental hospitals are stagnant and inactive with regard to treatment and that in them some patients get lost in the overcrowding and understaffing which exists there. Such patients may become chronically dependent, lose their motivation toward rehabilitation and also lose the interest of their families in their possible recovery. These things tend to produce an added disability on top of the patient's actual illness, with the final result often being a "long-term care" hospital patient. However, the modern public mental hospital does not have to be like that. Disability in addition to illness can be replaced by mobility in treatment, by healthy attitudes of the staff looking to early hospital release, by encouragement of continued family contacts for the patient and by the institution of active treatment on admission to the hospital rather than a month or 6 weeks after admission, as was formerly so often the custom.

It is difficult for me to encourage the Day Hospital as a separate treatment facility standing alone, and to this I think the authors would agree. However, even here, we must be careful to learn what each of us is talking about when we use the designation Day Hospital. Most writers on this subject consider the Day Hospital to be a facility for the care and treatment of patients who report daily and who spend some 7 or 8 hours in the unit. Patients have lunch in the unit, but are home for the night and for dinner and breakfast. On the other hand, some writers make no differentiation between the Day Hospital and the Outpatient Psychiatric Clinic. In some places the Day Hospital is a part of the public or private mental hospital and operates as a unit of such hospital. In other places the Day Hospital operates alone or in conjunction with a mental health center or otherwise.

The same variations in organization may be seen when we consider Night Hospitals and Halfway Houses. I think the major point here is that we should understand what we are individually talking about when we use such facile new names in our discussion of mental health programs.

In my judgment, many of the states like Missouri are now making prodigious efforts to improve their long stagnant and outmoded state mental health programs. Such concepts as these we are discussing here today are but new ways to approach old problems. Most of these ideas and innovations were not born in America, but came to us from other countries. I believe we should distill and make practical these ideas in the true American custom and then be willing to institute such new programs as will proper-

ly add to our modern therapeutic armamentarium. We should not adopt these ideas just because they are new or novel in character. They should also be practical and usable in the situations for which we recommend them. If they are not, then we are surely not justified in asking for public money for their support.

I appreciate the privilege of discussing this interesting paper, but I, too, am more interested in meeting the mental health needs of our communities by the broader concepts and methods inherent in mental health centers—such as the authors describe—than I am in the operation of separate and distinct Day Hospital units alone. Such mental health centers may include a variety of psychiatric services, in addition to the Day Hospital. These are the Night Hospital, the Halfway House, the Outpatient Clinic, the rehabilitation unit, and consultative and educational services to the community in specific as well as in general areas. Within this broad conceptual framework each community may include those mental health services which it needs and can afford. This adjustability feature provides a strong argument in favor of the mental health center. Also, the breadth of services which it provides gives hope that in the foreseeable future we may see the development of more and more Health Centers—rather than just mental health centers—where the problems of the whole person may receive proper attention and where public health and mental health may join forces for a better life for all our citizens.

Dr. Charles Watkins, New Orleans, La. Drs. McNichol and Seale are to be congratulated upon their presentation. It is an unusually comprehensive survey of the literature and a well-organized presentation of the facts about their own treatment center. Having had considerable personal contact with their center, I would also like to congratulate them on their achievements.

They have raised a number of points in their paper that are worthy of further discussion, and perhaps a friendly skepticism. I cannot help but wonder if the "renaissance of thought" which they describe is more imagined than real. I cannot help but remember that the New York State Hospital system prior to World War II offered in very limited degree some of the things that are considered new today. Is it possible that the greatly increased number of psychiatrists now available in the smaller communities is causing some of the changes that we attribute to the "new outlook"?

I am interested in the figures presented in table 1. Of 300 patients listed, 187 were either psychoneurotic or sociopathic. If all other patients would have required admission, it would have taken 87 of these patients to bring the estimated commitment need up to 200. This seems very strange to me as I remember the small number of individuals with these diagnoses I have seen committed.

On table 2, I see that some patients have progress interviews and others have psychotherapy sessions. The authors make a time differential in these sessions. Do they mean that the 15 minute sessions were not psychotherapeutic? Are they indicating adherence to the sanctity of the analytic hour?

I am not clear as to the method of estimation of cost. Do they mean that if a patient were seen biweekly, the total cost of the treatment would amount to $14, figured as $1 per day for that period? If this is true, I would say their method of cost accounting leaves much to be desired. Of more value would be the cost per total treatment time of discharged patients. This would make it possible to compare the cost with the cost of hospitalization and the cost of private outpatient care. A cost of $14 per 15 minute "progress" interview does not appear to be particularly inexpensive.

Again I would like to compliment the authors. My questions are raised in the hope that they would afford the opportunity for further clarification.

Dr. McNichol (Closing). We were interested in presenting a comprehensive view of the Treatment Center realizing that it is not always possible to adequately cover such a broad topic in both breadth and depth when one must conform with space limitations.

We are not in disagreement with Dr. Duval with respect to the utilization of inpatient treatment. Certainly inpatient care is highly desirable and necessary in some cases.

Dr. Watkins raises several challenging points. First, he said, "I cannot help but wonder if the 'renaissance of thought' which they describe is more imagined than real." He suggested that the increased number of psychiatrists has contributed to the recent progress made in the field of mental health. With this we wholeheartedly concur. However, we believe that the philosophy of outpatient voluntary treatment of the mentally ill still represents "renaissance of thought" to a considerable extent and that it will continue to stimulate even further progress in the years ahead.

He also commented on the 200 patients whom he had considered to be likely candidates for commitment had our services not been available. The reply to this comment is surely determined by the commitment criteria of the hospitals in question. Our figures are accurate for this locale.

Our purpose in differentiating the "progress interviews" from "individual psychotherapy" was to enable us to better budget the time spent in treatment.

Cost of treatment is a difficult area to assess. We believe that most people in the field would agree that the treatment of a patient goes on continuously regardless of the frequency of interviews which perhaps only reinforce the treatment process. Therefore, it does not seem unreasonable to consider that the therapeutic process is offered to the patient on a daily basis so long as he or she is seen regularly by the physician or other member of the treatment team. Moreover, we suggest in this context that family members undoubtedly can and do become active, albeit unpaid members of the treatment team whenever they are offered sufficient support and encouragement by the professionals involved. We feel that this view tends to justify the cost accounting outlined in the body of this paper.

We are pleased that our paper stimulated so much interest and very much appreciate the comments made by both discussants. We trust that we have been able to offer further clarification and justification of our position.

CASE REPORT

Angioneurotic Edema from Sunlight

LT. R. NEAL SCHNEIDERMAN, MC, USNR,† *Beaufort, S. C.*

Introduction

ALLERGIES DUE TO PHYSICAL AGENTS such as cold, heat, pressure and light have been recognized for many years and were popularized by Duke.[1] Among this group of physical allergies, light is the one responsible for the most varied types of reactions. These reactions to light may be classified as follows:[2]

a. Polymorphous light eruptions.
   (1) Erythema with or without edema.
   (2) Erythema multiforme.
   (3) Eczema type.
   (4) Papular urticaria or prurigo type.
   (5) Chronic inflammatory plaque-like dermatitis.

b. Urticarial hypersensitivity to light.

Polymorphic light eruptions occur in people sensitive to light of wave lengths less than 3150Å., whereas the wave length spectra causing urticarial reactions cover a considerably wider range and those affected may be divided into three groups,—those sensitive to wave lengths less than 3100Å., those sensitive to wave lengths less than 3700Å., and those sensitive to wave lengths between 4000 and 5000Å.

The erythema type of polymorphous light eruption is characterized by an erythematous eruption of the face and neck that appears a few moments after exposure to light and disappears after a few minutes or an hour or two. Edema may or may not be present. More persistent eruptions, referred to as erythema multiforme type of polymorphous light eruptions or erythema solare perstans are characterized by discrete papular, multiform and urticarial lesions. These lesions must be differentiated from the evanescent, multiform lesions of lupus erythematosus.[3] The eczematous, prurigo and plaque-like types of polymorphous light eruptions differ sufficiently in clinical appearance from the eruption presented below as to obviate any confusion with them. Solar urticaria is characterized by whealing in areas of skin that are exposed to sunlight. Such whealing appears not more than a few minutes after exposure and disappears completely in a few hours.[4]

In the case presented, the patient developed an erythematous, edematous eruption of the areas of skin exposed to sun. The clinical picture presented, however, coincides with no one of the above described conditions.

Report of Case

The patient was an 18 year old, white United States Marine Corps recruit, who was first seen at the Dispensary, Parris Island, South Carolina. He was transferred to the U. S. Naval Hospital, Beaufort, S. C., with the following note:

"The patient has had two episodes of marked edema of the hands and face in his first 10 days of active military duty. He was treated with antihistamines and Adrenalin with poor response."

The patient stated that since the age of 6 a burning sensation developed in uncovered areas of his skin whenever he was exposed to sunlight. The symptoms were most marked in the spring and early summer and gradually diminished through the fall. He had at no time observed any skin changes associated with the burning sensation during or after exposure to the sun. He further stated that he always worked indoors and never frequented beaches. He never exposed himself to sunlight except for the short periods of time required by traveling from one enclosure to another. The patient had an appendectomy at age eleven. The remainder of the past history was not contributory. Several days after his arrival at Parris Island, the patient was given the routine immunizations consisting of smallpox vaccine, tetanus toxoid, typhoid and influenza vaccines.

The patient started his recruit training on Oct. 16, 1959. The first 10 days consisted of a considerable amount of marching. During this time the sky was clear and the temperature ranged from 85 to 95° during the day. The patient felt burning sensations

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The opinions or assertions contained herein are those of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

in areas of his skin exposed to the sun at the very beginning of his training, and by the end of the first week swelling of these areas would be produced by approximately one hour's exposure. This swelling was soon noticed by the drill instructor who sent the patient to the dispensary.

At the dispensary, the patient was treated for angioneurotic edema with epinephrine and an antihistamine. These drugs produced very slight relief immediately, and the edema had subsided only after 3 days. He then returned to his training platoon. The following day a similar episode occurred and the patient was transferred to the Naval Hospital.

Physical examination at the time of admission revealed marked edema and erythema of the face and hands. The remainder of the examination revealed no other abnormalities. Complete blood count, chest x-ray examination, urinalysis, BSP. test, thymol turbidity, total protein with A/G ratio, cephalin flocculation, L. E. preparation and 24 hour urine for quantitative porphyrins were within normal limits.

Clinical experiments. Determination of the sensitivity to the range of light wave length was done using the only filter available at the time, ordinary window glass, which filters out light of wave length shorter than 3200A. The patient was instructed to expose his skin to the sun through window glass. This was done and no reaction was obtained with up to 4 hours of exposure.

The patient was instructed to expose his hands to the sun without a filter for variable periods of time to determine the minimum time necessary to procure a reaction. At no time was it possible to produce a reaction when the skin was exposed for less than one hour. For periods of less than one hour no change in the skin occurred. For periods greater than one hour the only reaction that occurred was angioneurotic edema. Areas of the trunk were exposed to sun for periods up to 3 hours on several occasions with no reaction objectively or subjectively.

When the minimum exposure time was determined, the patient was instructed to expose himself repeatedly when the previous reaction had completely disappeared. This was done on 10 occasions. Each successive exposure required a greater time to produce the reaction. After the tenth exposure only erythema could be produced, and this only after 4 to 5 hours of exposure.

The patient was not exposed to sun for 7 days. At the end of this period the patient's reactivity had returned. Passive transfer tests were then performed, injecting the patient's serum into the skin of the forearms of a volunteer. One of the forearms was exposed to sun before the injection and one after the injection. These tests were negative.

Finally, several drugs were used in the hope that a suitable method of control of the patient's condition might be found.

1. Chloroquine[5] 250 mg. t.i.d. was given for a period of 5 days.

2. Pyribenzamine (tripelennamine HCl)[6] 50 mg. t.i.d. was given for a period of 6 days.

It was found that treatment with the above drugs did not alter the patient's reaction to sunlight.

Discussion and Summary

A case of angioneurotic edema due to a physical allergy to sunlight has been presented. This patient's reaction differed from the typical case of solar urticaria in the following ways:

1. The clinical sign was that of angioneurotic edema rather than urticaria.

2. The time of exposure required to produce the reaction was much longer than that seen with solar urticaria.

3. Relief from the signs of angioneurotic edema required several days, also much longer than that seen in solar urticaria.

The objective picture presented by the patient was clinically reminiscent either of the erythematous type of polymorphous light eruption with edema or of solar urticaria. The wave length sensitivity determined does not fall into the range of polymorphous light eruption and the time relationships do not correspond with those of solar urticaria. The exact classification of this case is not clear but it would seem that it would fit most closely with a delayed type of solar urticaria. The reaction both in the case presented and in solar urticaria in general is probably mediated by a histamine-like substance.[5]

Histamine content of human skin was found by Johnson[7] to be greatest in the areas of the eyelids and lips, areas which showed the greatest reaction in the case presented. It is interesting to note that no reaction could be produced on the trunk, an area of presumed lesser histamine content, even though prolonged exposure was effected. Explanation for the delayed and prolonged reaction in this case is not forthcoming.

The clinical tests performed suggest hyposensitization[8] by slowly increasing exposures to light as the most reliable method of control of the signs and symptoms of the case presented.

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T-3 Red Cell Uptake for Routine Thyroid Screening in a Community Hospital*

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This use of radioactive iodine may offer a satisfactory means of determining the level of thyroid function without the disadvantages of currently used tests.

In 1957 an *in vitro* thyroid function test using a radioactive isotope was introduced by Hamolsky, Stein, and Freedberg.[1] They demonstrated that human red blood cells combined with I^{131} labeled tri-iodo-thyronine so as to accurately reflect the thyroid status in man. Since that time several publications have supported their conclusions that this test would be a valuable adjunct in the laboratory diagnosis of thyroid function and/or its disorders. The purpose of this paper is to discuss our results with this test and to present slight technical modifications in its procedure.

Rationale

At the present time certain details in the physiology of tri-iodo-thyronine have not been clarified. Most investigators do agree, however, with several recently reported chemical and physiologic theories of thyroid hormone transport.[2-5] The thyroid hormones, thyroxine (T-4) and tri-iodo-thyronine (T-3), are primarily bound to a blood protein named thyroid-binding globulin (TBG) which migrates electrophoretically between $Alpha_1$ and $Alpha_2$ globulins. TBG combines with thyroxine preferentially to tri-iodo-thyronine. Therefore, in hyperthyroid states the TBG is relatively saturated with thyroxine. Tri-iodo-thyronine must seek other carrying sites. It has been shown that thyroid hormones also combine with erythrocytes in a similar manner as they do with TBG. This combination with erythrocytes is considered secondary to the combining sites with TBG. In hyperthyroid states combination with secondary sites is the only alternative for tri-iodo-thyronine. Therefore, it is apparent that there is an inverse relationship between the tri-iodo-thyronine bound to the erythrocytes and the amount of circulating available TBG.

In the *in vitro* test, when I^{131} labeled tri-iodo-thyronine is added to a blood sample from a hyperthyroid individual more of the hormone will be taken up by the red cells in that all the available TBG is saturated with thyroxine. Tri-iodo-thyronine cannot break up the combination of thyroxine with TBG. In a hypothyroid individual there will be a decrease in the uptake of the hormone by the erythrocytes since there is an above normal amount of available TBG.

Procedure

Six milliliters of whole blood are drawn and placed in a Vacutainer tube containing a balanced oxalate. A 3 ml. aliquot is then placed into a 10 ml. Erlenmeyer flask with 0.1 mg. of diluted I^{131} L-tri-iodo-thyronine (0.5 mc/cc. of I^{131} L-tri-iodo-thyronine is diluted 100 to 150 times with sterile isotonic saline). The flask is stoppered and sealed with paraffin. The samples are placed in a rotating water bath at 37°C. for two hours. After incubation 1 ml. of the patient's blood is placed in a test tube and the sample is counted in a well type scintillating counter. A correction is made for background radiation. Each specimen is then centrifuged at approximately 3,000 r.p.m. and the cells are washed five times with tenfold volumes of isotonic saline. The washed cells are then counted as described above. A Wintrobe hematocrit is determined. The percentage of red cell uptake is calculated as follows:

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$$\frac{\text{WRBC} \times 100 \times 100/\text{hct}}{\text{WBC}}$$

WRBC—net counts of washed red blood cells.

WBC—net counts of whole blood.

100/hct—hematocrit corrected to 100% for volume comparison.

Normal values: Male, 12-19%; female, 11-17%.

Duplicate samples have been processed, but the practicality of this technic is questionable, since it has been reported in one series that the difference between duplicate determinations ranges from 0.0 to 1.6%, with an average of 0.6 per cent.[6] We have also found that the differences between duplicate determinations has been less than 1 per cent.

Results

Four hundred T-3 red cell uptakes were performed in our laboratory from January 1960, to February 1961, on blood samples drawn from hospitalized patients, outpatients, laboratory personnel, etc. (Table 1). This number included 340 females and 60 males representing all age groups. Of these cases 73% fell within the normal range (male, 12 to 19%; female, 11 to 17%). Thirteen per cent (52) of the cases presented with abnormal values consistent with clinical status of either hypo- or hyperthyroidism. The remaining 14% (55 cases) presented with abnormal results not consistent with their clinical status. Thirty-three cases (8.2%) had values which were only 1% or less above or below the accepted range, or the abnormal results could be attributed to known interfering factors (Table 2). The remaining 22 cases (5.5%) had abnormal results which did not coincide with the clinical findings nor could interfering substances be found.

TABLE 1

REPORT OF FINDINGS

Thyroid Status	*Cases*	*Per Cent Uptake*
Euthyroid male	46 (11.5%)	(12.0-19.0)
	12 (3.0%)	>19.0
Euthyroid female	245 (61.1%)	(11.0-17.0)
	36 (9.0%)	>17.0
	10 (2.5%)	<11.0
Hyperthyroid male	1 (0.2%)	25.5
Hyperthyroid female	26 (6.5%)	20.2-39.7 (25.8 average)
Hypothyroid male	1 (0.2%)	6.1
Hypothyroid female	8 (2.0%)	7.6- 9.9 (8.9 average)
Normal pregnancy	16 (4.0%)	7.5-10.3 (9.2 average)

TABLE 2

FACTORS WHICH MAY HAVE AN EFFECT ON THE T-3 RED CELL UPTAKE[7]

I. Decrease
- A. Pregnancy
- B. Estrogen
- C. Propylthiouracil in hyperthyroidism
- D. Iodide in hyperthyroidism

II. No (or slight effect)
- A. Thyroid enlargement—colloid goiter, nontoxic nodular goiter, thyroid carcinoma
- B. Exogenous iodine (except where iodide in amounts which cause a reduced hormone secretion is given)
- C. Anxiety
- D. Congestive heart failure
- E. Hypertension
- F. Administration of mercury
- G. Other endocrinopathies—diabetes mellitus, Addison's disease

III. Increase
- A. Anticoagulants—Dicumarol, heparin
- B. Nephrosis
- C. Severe liver disease
- D. Severe metastatic malignancy
- E. Severe pulmonary insufficiency with CO_2 retention
- F. Paroxysmal atrial arrhythmias

Discussion

Our results with the use of this test have been most gratifying. Approximately 94% of the patients studied in each category had results compatible with the clinical status. Determinations of protein-bound iodine (PBI.) and radioactive iodine uptake (RAI.) were frequently performed in conjunction with the T-3. The results of the T-3 correlated in 100% of the cases in which the result of the PBI. and RAI. were consistent with the clinical status. One of the really big advantages of the T-3 over the PBI. and RAI. is the fact that exogenous iodine does not usually significantly alter the results of the test. For example, abnormal PBI. determinations were observed in 12 instances in which the patients had had a cholecystogram. The T-3 findings in all cases were compatible with the clinical status of the patient. No correlation exists between the three tests when the results are within the normal range. For example, in the euthyroid state one may have a low-normal PBI. and a high-normal T-3.

It has been theorized that atmospheric carbon dioxide may slightly alter the pH of the blood and thus cause some elevation in the T-3 uptake. We believe we have partially obviated this interfering factor by drawing the blood samples in a Vacutainer test tube and by sealing the Erlenmeyer flasks with paraffin before incubation. Accurate results depend upon a day-to-day standardized procedure carried out

by a technician skilled in the use of isotopes. For example, any slight variation in the washing of the red cells or change in temperature during incubation will make for erroneous results.

In many respects this test is more convenient to the patient than other thyroid tests. The patient may come to the laboratory any time during the day since the blood can be tested up to 7 days if kept under refrigeration. Only one visit to the laboratory is necessary. The patient does not have to avoid exogenous iodine. Since radioactive materials are not injected or ingested, this test is of particular value when dealing with infants or with patients who fear ionizing radiation. The patient's clinical course can be evaluated by the test during therapy. Of interest is the observation that the T-3 is consistently decreased in the normal pregnancy. This phenomenon is usually first noted between the seventh or eighth week of gestation; however, it has been demonstrated as early as the third week.[6] From this time on all uptakes ranged between 7.5-10.3 (mean: 9.2). Normal T-3 results obtained after the eighth week have heralded a miscarriage in several cases. This observation may prove to be another value in the use of tri-iodo-thyronine.

Of all the thyroid tests offered, we have found the T-3 test to be most accurate and convenient for use in any community hospital laboratory using radioactive isotopes.

Summary

1. The results of 400 T-3 tests are presented.

2. The rationale of this procedure is discussed.

3. The details of the working procedure are presented with slight technical modifications.

4. Conclusions drawn from this series prove this test to be convenient and safe for the patient as well as accurate and economical for the laboratory.

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Failure of Gastric Cytologic Technic in the Diagnosis of Gastric Malignancy

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The purpose of this note is to indicate that gastric cytologic studies must be done under ideal circumstances to have value. By no means can the simple and valuable "Pap" smear technic for uterine studies be transposed to examination of the gastric mucosa.

THE VALUE OF CYTOLOGIC STUDY of exfoliated cells of the gastric mucosa in the diagnosis of malignant lesions of the stomach has already been indicated.[1-4] However, these authors have established gastric cytologic study as a specialized technic often employing special equipment, personnel, or methods in evaluating patients suspected of gastric malignancy. The purpose of this study is to evaluate the usefulness of this procedure when done by a group of persons without particular training or special interest in this field. The vast majority of the gastric washings were obtained by medical students and house officers on patients with upper gastrointestinal complaints, although some were obtained by members of the gastroenterology service coincident to the preparation of the stomach for gastroscopy.

Method

In general, the following procedure was carried out in obtaining material for study. The fasting stomach was irrigated with approximately 300 to 500 ml. of normal saline, the last 50 to 100 ml. being collected in an iced container to retard acid-pepsin digestion of the exfoliated cells. The specimen remained iced for 20 to 40 minutes before centrifugation in the hospital cytology laboratory. There the usual procedure was to prepare a cell block and two Papanicolaou slides if there was sufficient sediment, if not four Papanicolaou slides were prepared for study. These preparations were stained and reviewed in the usual manner by the cytology technician. They were classified as follows: Class I—absence of atypical or abnormal cells; Class II—atypical cytology but no evidence of malignancy; Class III—cytology suggestive of, but not conclusive for, malignancy; Class IV—cytology strongly suggestive of malignancy; Class V—cytology conclusive for malignancy.

The charts of 211 patients having 259 cytologic studies of gastric washings over the past 3 years were reviewed. The results are presented in tabular form (Table 1). Twenty-six patients had a histologic diagnosis of carcinoma of the stomach. Eight patients had probable carcinoma by x-ray, gastroscopy, or both. The remaining patients had no evidence of gastric malignancy. In particular the one patient in the noncancerous group who had a Class IV Papanicolaou smear has for 3 years subsequent to that study shown no evidence of gastric malignancy.

Discussion

The results indicate that gastric exfoliative cytology is of no value when utilized by a large number of unselected hospital personnel. However, this should not condemn this method of examination but should demonstrate that gastric cytologic study cannot be readily adapted for the general usage that has been applied to the study of the cervix and vagina for malignancy. Authors reporting good results with gastric cytology have been careful to emphasize the necessity for extreme care in obtaining and processing the material for study. These authors included expressions noting the need for "a well trained cytologist,"[3] and "careful rapid collection and processing of the material by well trained, interested personnel."[4] That irrigation technics alone have not sufficed for some in the diagnosis of gastric malignancy is further shown by the development of such apparatus as abrasive balloons[5] and the Ayre brush.[6] In addi-

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TABLE 1

TABULATION OF GASTRIC CYTOLOGIC STUDIES ON 211 PATIENTS

	No. of Patients	*No. of Cytologic Studies*	*Unsatisfactory*	*I*	*II*	*III*	*IV*	*V*
Proved cancer	26	29	5	21	1	1	1	0
Probable cancer	8	8	2	4	0	2	0	0
No cancer	177	222	20	193	6	2	1	0

tion, various buffers and enzyme solutions have been recommended in an effort to improve the reliability of the method.

Our failure to obtain a high percentage of positive cytologic examinations may have resulted from a number of factors. Among some of the possible explanations are: the varied personnel collecting the specimens, lack of vigorous irrigation of the stomach, failure of icing of the material to sufficiently retard digestion by the gastric fluid, failure to promptly centrifuge the washings and prepare the slides, and unfamiliarity of technologists with abnormal cells. Whatever the factor or factors involved in our failure to find malignant cells in a reasonable number of those patients with proven or probable malignancy of the stomach, the observation that this method of study is not adaptable for routine hospital use appears to be valid. Because of the time and personnel involved in the adequate performance of gastric cytologic study, the procedure does not appear adaptable as a method of screening for cancer of the stomach.

If the pitfalls of this technic are not recognized, a false sense of security may be established by a series of negative cytologic examinations. It should be apparent that negative studies do not conclusively exclude the diagnosis of gastric malignancy. Since so large a number of our patients with negative cytologic studies include those with known cancer, it would appear important to limit this type of study to a select group of patients by a select group of personnel who are particularly interested in assuring that gastric cytologic study can be a valuable adjunct to the diagnosis of gastric malignancy.

Conclusion

Evidence is presented which further emphasizes the observations of others that cytologic study of gastric material for malignancy requires specialized attention in obtaining and processing the material and is not adaptable as a routine hospital procedure or as a means of screening for gastric malignancy.

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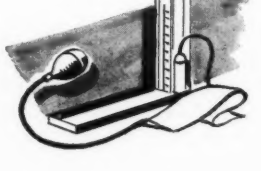

The Problem of Anesthetic Overdosage

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After outlining the hazards of overdosage of both anesthetic and relaxant agents, especially in the patient who is a poor operative risk, the author pleads for better communication and understanding between surgeon and anesthesiologist so this hazard may be avoided.

OVERDOSAGE WITH ANESTHETIC AGENTS is frequently indulged in by anesthesiologists and demanded by surgeons as a substitute for satisfactory technics in surgery or anesthesia. Such a problem is especially acute in the poor risk patient but it is, by no means, a rare occurrence in more robust individuals undergoing surgical operation and anesthesia.

Discussion

When intra-abdominal procedures are performed a "state of relaxation" is required. This implies complete loss of muscle tone, complete looseness of the peritoneum, a minimum or absence of active respiratory movements and a contracted bowel. Surgeons desire and need relaxation to expedite the surgical procedure. This should be provided if it does not compromise the safety of the patient. Unpleasant operating conditions associated with poor muscle relaxation may not be immediately apparent to the anesthesiologist. On the other hand the surgeon may blame mechanical or anatomic difficulties on the conduct of the anesthesia. Moreover, when ideal working conditions are achieved only at the cost of overdosage, then the patient is subjected to an additional and unjustified risk.

Patients react differently to similar amounts of drugs. What may be anticipated as a modest dose for a particular patient, may actually produce such dangerous side effects as depression of respiration and cardiovascular collapse. This state of anesthetic overdosage places severe strain on the physiologic mechanisms of all patients but is most likely to occur and be poorly tolerated by the patient undergoing emergency surgery. Surgeons and anesthesiologists must balance the risk of anesthetic overdosage in the individual patient against the desirability of working conditions which may expedite this particular surgical procedure. Only by developing mutual understanding, tolerance, and communication, each with the other, can both anesthesiologist and surgeon find a satisfactory solution without subjecting the patient to unnecessary risks.

With the introduction into anesthesia of muscle relaxant drugs, which provide relaxation equal to that achieved by deep planes of general anesthesia or by spinal anesthesia, there has developed a tendency to substitute overdosage of these muscle relaxing agents for imperfect working conditions associated with poorly conducted inhalation anesthesia. Such unsatisfactory surgical conditions may, in fact, not be due to inadequate amounts of muscle relaxant. All drugs producing muscle relaxation of a sufficient degree to facilitate the performance of surgical procedures also produce profound depression of respiration. If such patients are not adequately and vigorously ventilated, either by manual or mechanical methods, there develops a marked retention of carbon dioxide. This situation may be directly responsible for overdosage with anesthetic drugs, especially during intra-abdominal operations. As carbon dioxide accumulates an increasing degree of muscle tone develops. This makes surgical manipulations most difficult if not impossible.

Such a situation is often improperly evaluated and the cause believed to be due to either an improper depth of anesthesia or to inadequate amounts of muscle relaxant. More muscle relaxant drug or deeper planes of general anesthesia are then provided in an attempt to overcome this increased muscle rigidity, there-

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by producing plasma levels of drug much above that needed in the presence of proper ventilation. This causes further depression of respiration with further increase in retention of carbon dioxide and an even greater degree of muscle tone. Thus, a vicious cycle develops in which improper conduct of anesthesia causes more difficult operating conditions leading directly to overdosage with anesthetic drugs.

Reports by Dundee[1] and by Gray and Rees[2] have shown the need for much less muscle relaxant drug when patients are subjected to vigorous ventilation. Bonvallet[3] has suggested that increased blood tensions of carbon dioxide produce an excitatory effect on the ascending activating reticular system, and that hyperventilation with a production of lowered blood carbon dioxide tensions diminishes reticular activity. Thus, strict attention to proper ventilation and the prevention of an increased blood tension of carbon dioxide are of the utmost importance in preventing overdosage with all anesthetic agents.

Surgeons have begun to expect a degree of relaxation that can sometimes only be provided by gross overdosage with muscle relaxant drugs or by unnecessarily deep planes of general anesthesia. This situation is neither desirable nor necessary from an anesthesia or surgical point of view. The ability to perform surgical procedures under somewhat less than ideal conditions may prove advantageous to the patient. Often in the individual in whom it is most difficult to produce complete relaxation one has a patient most prone to react poorly to relaxant drugs or to anesthetic agents. By reasonable cooperation between surgeon and anesthesiologist, the lightest plane of anesthesia for a given procedure may be achieved, to which may be added profound muscle relaxation needed at the moment by the surgeon. This is much more desirable than unnecesarily deep planes of anesthesia or profound muscle relaxation throughout the entire procedure. Only in this way can satisfactory surgical conditions be provided without overdosage of the patient.

The patient with a chronic illness or a late stage of acute surgical illness who is in electrolyte imbalance must be approached with utmost caution when using muscle relaxant drugs since these patients often show bizarre reactions. However, these same patients are frequently operated upon in an extreme emergency with a minimal preoperative study and minimal preoperative correction of the underlying disturbances in the physiologic state.

The margin between the amount of agent adequate to produce satisfactory surgical working conditions and overdosage producing respiratory and cardiovascular depression may be extremely narrow. The patient in electrolyte imbalance, hypovolemia, or with critical surgical illness is often in a state of depression of vital homeostatic mechanisms. Such individuals may show profound respiratory and cardiovascular depression with a plasma level of drug that, in a normal individual, would be quite inadequate to produce satisfactory anesthetic and surgical conditions.

All known inhalant agents used alone to produce an adequate degree of muscle relaxation for satisfactory surgical conditions may require dangerously deep planes of anesthesia. Such amounts of potent volatile agents in the critically ill, depressed patient are most likely to produce adverse respiratory and cardiovascular responses. Therefore, the proper dose of anesthetic agent or muscle relaxant must be obtained by titration of extremely small increments added gradually until the desired effect is reached. Extra time must be taken to evaluate the response to the initial dose as well as to each additional dose of drug if overdosage and subsequent prolonged depression are to be avoided. Surgeons must be willing, when necessary for the welfare of the patient, to accept less than optimum relaxation if dangerous depression in the operative period is to be avoided. Such dangerously deep planes of anesthesia also result in a depressed state in the postoperative period which may directly contribute to such complications as atelectasis or cardiovascular collapse. These complications can best be avoided by having the patient awake and active at the conclusion of the surgical procedure.

Local or regional anesthesia might be expected to produce less extreme degrees of respiratory or cardiovascular depression in such problem patients who must be subjected to surgical and anesthetic procedures. There still exists, however, the danger of overdosage with all the known drugs used to produce local or regional nerve block. In attempting to produce local anesthesia over a large area, or to produce regional anesthesia in an area where many nerves must be blocked, the maximum

safe dose of an anesthetic agent may easily be exceeded. Dangerous responses in the central nervous, cardiovascular and respiratory systems are likely to occur with such toxic amounts of anesthetic drug. The elderly, poor risk patient, in fact, is especially likely to show adverse responses to plasma levels of these drugs which would be considered most modest in the normal, good risk surgical patient.

Patients who have received an anesthetic still have a considerable residual plasma level of drugs for several hours in the postanesthetic period. At this time additional amounts of drugs have an additive effect to these residual amounts of anesthetic agents. However, such individuals often require relief of pain during this period. Narcotic drugs are likely to have a profound effect and the usual dose of a narcotic, under these circumstances, may cause extreme respiratory and cardiovascular depression or even narcotic poisoning, requiring resuscitative measure including the use of narcotic antagonists. Drugs given during the critical postanesthetic period should, therefore, be reduced to extremely small increments. By giving them intravenously an adequate period of observation, such as 5 or 10 minutes, permits the addition of further increments, if necessary, until the desired therapeutic effect is achieved. The elderly, debilitated or poor risk patient is most susceptible to this type of overdosage. Equivalent amounts of drugs tolerated by the same patient at another time may now prove to be quite inappropriate and lead to severe respiratory and cardiovascular depression.

Summary

Excessive doses of anesthetic agents are often incorrectly used as a substitute for adequate technics of surgery and anesthesia.

Inadequate and improper ventilation may play a major role in the production of anesthetic overdosage.

The poor risk, debilitated surgical patient operated upon in an emergency is especially prone to react poorly to such overdosage.

Ability to satisfactorily perform surgical procedures under less than ideal anesthetic and surgical conditions may prove advantageous to the patient.

A plea is made for greater communication and cooperation between surgeon and anesthesiologist in approaching the surgical and anesthetic management of such problems.

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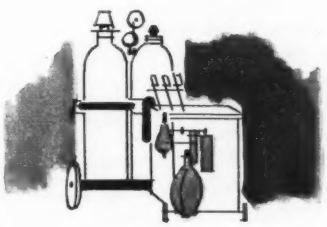

Clinical Impressions on the Use and Value of Chlordiazepoxide in Psychiatric Practice

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This drug is not as innocuous as is implied. Its use may be attended by ataxia resulting in falls, paradoxical psychologic reactions as well as a change in driving habits resulting in auto accidents. These and other reactions have been reported. This drug then should be used only by psychiatrists who choose the indication for use.

I ORIGINALLY STUDIED the effectiveness of this drug* in twelve patients with severe anxiety, in collaboration with Tobin, Bird and Boyle.[1] In November 1959, the study was expanded to 30 patients. As in the original study the patients treated were selected from my private practice and from patients seen at the Henderson Clinic, Ft. Lauderdale, Florida.

Method of Study and Case Material

All patients with severe anxiety who were not frankly psychotic were included in this expanded study. (Four patients having schizophrenia and who were treated with chlordiazepoxide, as well as a small group of depressed patients who were treated with the drug in conjunction with amino-oxidase inhibitors, will be discussed as an adjunct to this paper.) The symptoms and degree of disability of each patient were noted but played no part in the initial selection for treatment. The 30 patients included 16 women and 14 men, the ages ranging from 22 to 52 years. The duration of illness ranged from 3 months to 13 years. Patients with physical symptoms were studied by laboratory methods; no abnormalities were found among those so studied. Routine laboratory studies were discontinued unless there was some special indication because experience showed there were no significant changes.

All patients were started on the same dosage scale. Each patient received one 25 mg. capsule of chlordiazepoxide at bedtime for the first two days; on the next two days a 25 mg. capsule was taken at 12 hour intervals, the first upon arising; after that a 25 mg. capsule was taken at 6 hour intervals, the first upon arising. At the end of this period each patient was evaluated as to progress with this therapy. No other drugs were used during this period except for the occasional use of a sedative at bedtime.

At the end of a 4 week trial period each patient was statistically grouped according to mental disorder and concomitant symptoms, using the Diagnostic and Statistical Manual classifications. The patients fell into the following diagnostic groups: 4 schizophrenic patients who, as stated earlier, will be discussed separately; 8 incipient schizophrenics (pseudoneurotic); 15 psychoneurotic patients, and 3 patients with personality trait disorders, passive dependent type. At the same time each patient was rated as to degree of improvement of the disability. (See Table 1.) All 30 of the patients exhibited anxiety and tension. There were 9 patients with phobic

TABLE 1

IMPROVEMENT ACCORDING TO DIAGNOSIS

	A	*B*	*C*	*D*	*E*	*F*	*G*	*Totals*
Psychoneurotic	1	5	3	1	3	2		15
Personality trait disorder						3		3
Chronic undifferentiated schizophrenic, incipient		2	1	1	2	2		8
Schizophrenic					1	3		4

A—complete relief
B—marked relief
C—significant
D—appreciable relief
E—slight relief
F—no relief
G—worse

*Librium supplied by Roche Laboratories, Division of Hoffmann-La Roche, Inc.

symptoms, 2 with hysterical acting-out, 2 with lethargy and fatigue, and one each demonstrating obsessive compulsive symptoms and physical concomitants. Each similar group was then evaluated for the effectiveness of chlordiazepoxide in alleviating the symptom. The rating scale for improvement in this study was the same as used in the original study with Tobin and associates. Patients who were rated as unchanged in their over-all reaction to the drug at the end of the 4 week trial were taken off it and dropped from the study. (See Table 1.) Three schizophrenic patients and 3 with personality trait disorders, 2 each of chronic undifferentiated schizophrenias, incipient, and psychoneurosis were dropped from the study.

The rating scale is as follows:

Excellent: complete or marked relief of symptoms and significant improvement in the patient's over-all adjustment, if this had been seriously affected by the disorder.

Good: significant relief of symptoms in either degree or frequency or both.

Fair: appreciable relief of symptoms in either degree or frequency or both.

Negative: symptoms not changed or slightly improved.

Condition worse: symptoms aggravated.

The subjective improvement of the patient was also noted according to the patient's own appraisal of the situation using the following rating scale that had been used in the first study also:

Complete relief: no discomfort and no perceived anxiety.

Marked relief: minimal discomfort and minimal perceived anxiety, usually limited to specific situations.

Significant relief: slight anxiety and slight discomfort.

Appreciable relief: improvement clearly recognizable as difference of degree of discomfort and perceived anxicty.

Slight relief: improvement barely recognizable as difference of degree of discomfort and perceived anxiety.

No relief.

Aggravated condition.

The subjective appraisal of the patient was then compared with that of the clinical investigator's rating and they were both found to be essentially the same.

Results

Since my findings concerning amelioration of symptoms and the subjective findings of the patients themselves showed almost 100% correlation, table 2 will clearly indicate the degree of improvement shown in each instance. One patient showed complete relief from anxiety, 7 marked relief, 4 significant relief, 4 appreciable relief, one had slight relief and 10 no relief. The same figures were true of tension. Of the 9 patients exhibiting phobic symptoms, one had complete relief, 4 marked relief, 2 significant relief and 2 appreciable relief. Of the 2 showing hysterical acting-out behavior, one had appreciable relief and one no relief. Of the 2 patients suffering from lethargy and fatigue one showed significant relief and one appreciable relief. The one patient with obsessive compulsive symptoms had significant relief and the one patient with physical concomitants showed no relief.

TABLE 2

IMPROVEMENT ACCORDING TO SYMPTOM

	A	*B*	*C*	*D*	*E*	*F*	*G*	*Totals*
Anxiety	1	7	4	4	4	10		30
Tension	1	7	4	4	4	10		30
Phobic reaction	1	4	2	2				9
Hysterical acting out				1		1		2
Lethargy and fatigue			1	1				2
Obsessive compulsive reaction			1					1
Physical concomitants						1		1

Rating scale same as table 1.

Side-effects suffered by the patients in this study were few in number and minimal in intensity. It had been noted in the original study that drowsiness was the side-effect most often reported. In that study dosage had been begun at one 25 mg. capsule per day upon arising. For the first few days a number of the patients complained of increased drowsiness which soon abated. In the expanded study, by starting the patients with a dosage of 25 mg. at bedtime for the first two days the drowsiness was largely eliminated. The only other side-effect noted in these 30 patients was an increase in verbosity and ability to express hostility which was rarely of sufficient intensity to cause discomfort to the patient. In one patient therapy was discontinued at the end of one day because of a dissociative reaction. Later she was again tried on chlordiazepoxide at a dosage of 10 mg. The dissociative reaction did not occur this time and some improvement was shown.

Throughout the study the patients continued in psychotherapy, since it was thought this

was the optimum method by which to observe the effectiveness of the drug and to augment its benefits.

At the beginning of the study each of the patients was evaluated numerically according to ability to work and again after the 4 week trial period of therapy with chlordiazepoxide. As seen in tables 3, A and B the following rating scale was chosen:

III Inability to work

II Working below levels prior to illness

I Working at usual capacity although exhibiting symptoms.

Patients who were rated as unchanged and in whom treatment was discontinued were not included in this rating. It should be noted that none of the patients who had been treated with other psychopharmacologic agents had responded in the desired manner. As shown by table 3, 11 of the patients, prior to taking the new drug, had been incapacitated for work, and 9 were working below prior levels. After 4 weeks of therapy, 9 of the 11 incapacitated for work were again working at their usual level and one was working but at a lower level and one remained incapacitated. Of the 9 working at a lower than their usual level, 8 were again up to par and one remained unimproved. Thus, out of 20 patients, 17 showed considerable improvement in work capacity, one showed slight improvement and 2, although improved in symptoms, showed no improvement in work capacity.

TABLE 3, A

IMPROVEMENT IN ABILITY TO WORK

	III	*II*	*I*
Prior to Librium	11		
After 4 wks. of taking Librium	1	1	9

III—unable to work
II —working below levels prior to illness
I —working at usual capacity though showing symptoms

TABLE 3, B

	II	*I*
Prior to Librium	9	
After 4 wks. of taking Librium	1	8

II —working below levels prior to illness
I —working at usual capacity though showing symptoms

Discussion

Based on the reactions of the patients in these studies, it would appear that chlordiazepoxide may be the much needed and long awaited medication for use in the psychiatric treatment of the psychoneurotic patient with high levels of anxiety and tension. These patients responded the best of any studied. The response is almost immediate; both the anxiety and tension are rapidly reduced and the patients' drives tend to approach normal. This is especially noticeable in the case of the psychoneurotic patient with a phobic reaction. Ten patients having phobic reactions were treated in this series. Within 24 hours of starting on the drug (Librium) each had shown some improvement in his anxiety and tension. Not one of the 10 failed to show some improvement in symptoms. One patient in this group had been suffering from a phobic reaction for 13 years; within a day he was symptom-free and has remained so for the past 6 months while on a minimum dosage of the drug. It should be noted that these patients make no claim to having lost their phobias. It is simply that they are no longer of such pressing importance. As an adjunct to psychotherapy chlordiazepoxide also presents benefits to these patients. They find that, with their anxiety reduced, they are much more prone to verbalize their problems than they had been prior to this. They also showed a greater ability to express anger while under medication. Although many patients in this group become symptom-free and achieve a state of function which may have been lacking for some time, it is believed wise to continue the patient in psychotherapy for the best results to be obtained. It is interesting to note that when chlordiazepoxide is given to those with a normal level of anxiety it seems to promote a loss of drive to a rather marked degree. This is in considerable contrast to the highly anxious patient whose drives more nearly approach normal when taking the drug.

Three patients suffering from personality disorders of the passive dependent type and who were so dependent they had lost their ability to function and showed extreme panic, did not respond to the drug. In these patients there was the distinguishing factor of personality maldevelopment and relatively little anxiety.

There can be no generalization in regard to dosage. It must be individualized according to

the patient, symptomatology and diagnosis. However, certain basic steps should be followed. The following has been found to be an effective schedule: one 25 mg. capsule a day for two days, on the third day an increase to two 25 mg. capsules a day at 12 hour intervals, on the fifth day an increase to three 25 mg. capsules a day at 6 hour intervals. Taking the one a day 25 mg. capsule at bedtime seems to alleviate the early side-effects of drowsiness and facilitates sleep. When drowsiness is a side-effect it rarely seems to last past the second day of medication except in the case of the combination of an antidepressant and chlordiazepoxide. In my study of psychiatric patients, between 50 and 75 mg. has appeared to be the optimum dosage, although one patient has need to be continued on 100 mg. to maintain a feeling of well being. When the dosage is greater than necessary, the anxiety seems to increase due to the effect of the drug. Most patients after a period of roughly one month may gradually have the dose reduced to 25 mg. and continue to have relief of symptoms. One patient has had the dose reduced to 10 mg. per day and remains symptom-free, although he suffered severe anxiety, tension and phobic reaction for 13 years prior to taking the new drug. It seems likely that maintenance may be possible with other patients on this dosage, although this is not conclusive at this time. At the other end of the scale there is a patient who has needed 75 mg. of the drug for 6 months to remain symptom-free. Although these dosages hold good for the most part, it is also true that as the patient's level of anxiety fluctuates so does the requirement of the drug dosage change. It is well for the patient and the physician to be aware of this fact so adjustments can be made in accordance with the patient's needs. It thus becomes apparent that dosages both for optimum effect and maintenance need to be carefully individualized as previously stated. There appears no addiction to the drug, though there is a tendency to develop dependency upon it. Between 24 and 36 hours after withdrawal of the medicine there is a recurrence of symptoms, but without other untoward manifestations.

In the treatment of schizophrenics the drug seems to be somewhat less effective, although it does have some value. It is of no value to the patient who is actively psychotic. However, patients who have recently experienced psychotic episodes, who are in therapy, and have reached a point in their recovery where they appear to be psychoneurotic schizophrenic seem to respond. When the same patient under stress suffers disorganization of his personality, the drug no longer seems effective. The case of M. L. is a case in point:

M. L., a young man of 24, had recently had his first psychotic break. He suffered from paranoid delusions and had some auditory and visual hallucinations. Under therapy he had progressed to the point where he appeared to be a pseudoneurotic schizophrenic. At this point in therapy he was placed on Librium. He was started on a dose of 25 mg. and advanced to 75 mg. over a period of 5 days. The results were immediate and beneficial. His anxiety diminished appreciably and he was able to do things which he had not been able to do before, such as sit quietly and read for several hours. Prior to this he had not been able to sit quietly for longer than 15 minutes at a time. He also found that release from tension enhanced his ability to play the guitar. All in all he felt more relaxed and in control of himself than he had for many years. However, under stressful conditions in the home and in his personal life, he slid back beyond his previous condition. The drug seemed neither able to prevent this, nor able to make him more comfortable at this time.

Two patients who were overtly psychotic at the time the drug was used were not responsive and the drug was discontinued at the end of a trial period.

Often persons suffering from acute anxiety find it impossible to function in a normal fashion. They find it difficult, if not impossible, to move into the world or to socialize. This inability to function normally, brought about by intense anxiety, in turn causes the patient to become depressed. This type of depression can be lifted by the use of chlordiazepoxide. This lifting of the depression is brought about by lowering the patients' anxiety, thereby allowing them to return to a more normal way of living. However, it has been my experience, that the endogenous, or inward depressions, are not benefited by the drug.

Case Histories

It might be interesting to describe in some detail the cases of 2 of the patients treated with chlordiazepoxide.

Case 1. W. F. is a man of 40 years of age. He had been suffering from a high level of anxiety with phobic reactions for 10 years prior to treatment with Librium. During this period he had been in psychotherapy on an hour a week basis and had been given tranquilizers of various types without improvement. In fact his condition worsened over the years until he could no longer work. Finally the situation became so bad he could no longer be persuaded to leave his home to keep his ap-

pointments at my office. The financial worries engendered by not being able to work only increased anxiety and tension. Needless to say, his relationship with his wife and children worsened also as anxiety increased. In June 1959, Librium was started with a gradually increased dosage. Within 48 hours the patient reported improvement in his feeling of well being. "I know the problems are still there, but they don't seem to matter so much." Within a week he reported that he had left home for the first time in months and had gone to call on a neighbor by himself. He continued to come for hourly psychotherapy and it was noted that he was better able to ventilate some of his hostility than he had been heretofore. At the end of a 4 week period on 75 mg. of Librium per day the patient had progressed so he would drive the car alone, go shopping and visiting. At this time the dosage of Librium was gradually decreased until he was only taking 25 mg. a day. During this time he continued to make progress.

It was during this second 8 week period that, unfortunately, our supply of Librium ran out. Since this patient was one of the first patients treated with Librium, we undertook to see what the effect of placing him on a placebo would be at this time. Within 48 hours he phoned the office to report that for some reason the capsules were no longer as effective as they had been before. During the following few days many of the original symptoms returned. By the end of one week we again had a supply of Librium and Mr. F. was again put on 25 mg. a day. During the second 4 weeks of therapy Mr. F. felt sufficiently recovered to attempt to find a job, which he was successful in doing. As of this writing, some 10 months after commencement of Librium therapy the patient is still employed, his home relationships are greatly improved and he is only coming in for therapy for one-half hour every other week.

Comment. The rapidity with which the drug was effective has been noted in every case where it has been effective at all. As our charts show, not every patient showed such marked improvement, but in patients with high levels of anxiety it seemed to produce more dramatic and more complete relief than in any other type of reaction. In summary, we had a man who was completely disabled by anxiety returning to a relatively normal and stable method of living within the brief period of 2 months of therapy with chlordiazepoxide.

Case 2. J. P., a man of 22 years, was first seen in the fall of 1958, when he exhibited a high degree of anxiety with phobic reactions. He also had some somatic complaints as an inability to catch his breath from time to time. He was most fearful of leaving the home without his parents and, as a consequence, remained in the home much of the time, since both parents were employed. Although he knew something about TV repair work he was unable to bring himself to try to get a job In fact he was unable to even work part-time in the shop of a friend who had requested his help in meeting the emergency needs in his shop. From the fall of 1958 until June 1959, when the patient was started on Librium, he was seen twice weekly for psychotherapy and was also placed on a tranquilizer. Under this regimen he had started a formal course in TV repair work but was progressing very slowly. He was still unable to remain out of the home and away from his mother for any length of time.

In June 1959, the patient was started on the usual dosage of Librium, gradually increasing the dosage to 75 mg. Almost at once he noticed a marked diminution in anxiety. He was maintained at this level for 6 weeks and gradually the dose was reduced to a maintenance dose of 10 mg. per day. During the ensuing 6 months Mr. P. finished his course in TV repair work, obtained part-time work in this field and finally obtained a full-time job in a TV repair shop. The patient achieved these goals despite several traumatic, anxiety-producing events. His grandmother, to whom he was devoted, died during this period as did both his father and mother. These deaths occurred approximately at two month intervals, the mother having just recently died. Until this recent bereavement Mr. P. has been maintained in a state of equilibrium by increasing the daily dosage of Librium to 50 mg. and continuing with the once weekly psychotherapy sessions. It is almost too early to tell what the final effects of the mother's death will be. For the moment, however, the patient is continuing to function on the above regimen. It should be noted here that about 8 months after having begun the Librium therapy the patient decided to discontinue the drug without consulting anyone. He remained normally functional for three days, gradually his anxiety increased, and on the night of the seventh day without medication he became panicky when alone in the home and had to be given sedatives in the emergency room of one of the local hospitals.

It is believed that Mr. P. would, in all likelihood, never have been able to achieve the goals he has, had it not been for Librium. If, in the face of all the adverse circumstances that have arisen, Mr. P. is able to consolidate these gains, it will indeed be a victory for him and for Librium.

Summary

It is thought that chlordiazepoxide (Librium) may be the medicine of choice for psychoneurotic patients with high levels of anxiety and tension. Its value in psychoses is generally doubtful, but it does alleviate anxiety where this symptom is a component of the disorder. Although, as noted above, there do not appear to be any harmful side-effects from the drug, strict individualization of dosage should be observed to obtain the optimum in benefits. It is also believed the patient should continue in psychotherapy at this time.

Acknowledgment: The author wishes to express his gratitude to Power H. Sharretts, M.A., Research Assistant, for her valuable assistance in the conduct of this study.

Henderson Clinic

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EDITORIAL

THE MEDICAL SCHOOL'S RESPONSIBILITY TO THE COMMUNITY

The recent issue of the *Southern Medical Bulletin* was given over to a brief description of the medical schools of the South, a catalogue of which we may justifiably be proud. Since the *Bulletin* was to reach all the doctors of the area encompassed by the Southern Medical Association, the Editor seized the opportunity to acquaint those not in academic medicine with the problems which face medical educators currently and to some extent in the foreseeable future. Too often, as time removes us from our university days, we continue to believe that life and thinking at the college or university move on under the campus trees unchanged. So the Editor's purpose was to point to the dynamic life and faculty of today's medical colleges and the problems which inevitably accompany progress.

In addition to a scanning of some of today's problems in medical education, your Editor wished he might touch upon another aspect of the medical school, but space did not permit it. In some respects this side of the story is probably of more immediate interest to the practicing physician than the problems of the medical educator. This topic is what, if any, part the medical school should play in the community, whether the community be defined as a city or as a state. The acceptance of responsibility to the community by medical educators varies from a full sense of duty to a frank denial of any responsibility. Broadly speaking, the state school accepts an obligation to the community as part of its function, a philosophy understandable in the knowledge that support by tax money makes it more a servant of the people. Conversely, the privately supported school is often less aware of this responsibility even to the point of ignoring it. (Nevertheless it goes without saying that this is a generalization with exceptions a certainty.)

Citizens in our country generally concede that they have an obligation to the community in politics and in civic affairs, whether cultural or social. As certainly as these are duties of the citizen, the medical school has its responsibility to the community both to its medical profession and even more so to the health of its people. It is the center from which should emanate newer knowledge and its application for the common good. A school which sees itself as having served its function when it has conferred the M.D. degree, and possibly has included the training of a handful of specialists in its hospital facilities, should look at itself carefully. Actually it has shown itself to have gun-barrel vision. On the other hand there is the school with the vision or concept that the research within its walls and the knowledge of the new among its faculty should be and is available to the practicing medical profession and to the people of the community.

Such a concept might be implemented in a dozen different ways. Not only should the medical school teach physicians and those responsible for the laboratories of community hospitals new technics, when their practicality has become established, but should be available as consultants to assist in solving questions in technic or interpretation. Examples of such potential contributions would run into the dozens, if catalogued, for the fields of biochemistry, pathology and toxicology. The Record Room, the Department of Radiology and the Cardiopulmonary Laboratory might and should assist the smaller community hospital in its efforts to better the care of the patient.

It is nothing short of amazing to find at times a medical school which prides itself upon the education it gives its undergraduates, and at the same time closes its doors when it comes to the matter of graduate education, selfishly and jealously withdrawing from aids and duties which would guarantee better medical care generally. Your Editor over the years has been unable to fathom the not infrequent paradox of an Alma Mater conferring a degree and bidding the alumnus goodbye with a smile and a pat on the back, thereafter offering no more than an outstretched palm at times. It takes the vision and sense of responsibility of a University of Michigan and a Kellogg Foundation, for example, to develop a house-staff program which reaches to the far

corners of the state and which is paid for in lives saved and illness deferred, shortened, or controlled. Even though such results cannot be put in actual numbers, the evaluations of the program indicate that the care of the patient has improved greatly.

In the area of continuing or postgraduate education the responsibility of the school to the community has been more clearly defined, thanks to the American Academy of General Practice. Its program of continuing education for its membership was not to be gainsaid. By its size, this organization on a state basis can exert a pressure to which a tax supported school must listen. As a result there have developed and continue to develop excellent programs of continuing education in a number of schools in the Middle West and South particularly. In all fairness it should be said that not all such programs resulted from political pressure. We know intimately the evolution of certain postgraduate programs as the result of the vision of a school's faculty years before the Academy of General Practice was even a dream. One may actually suspect that programs initiated by certain state schools may have given birth to the idea of the Academy or at least have influenced its development. That continuation education has improved the medical care in this country is incontrovertible, when measured in such terms as better diagnosis and referral for specialized care.

One may anticipate that medical schools will be called upon to collaborate more and more in activities within the community. As increasing federal funds are made available to the medical schools one may well foresee strings tied in terms of contribution to the general good. It is unfortunate that human nature is such that vision may come only by coercion which belies the excuses of lack of time or facilities, expressions merely of apathy and mental laziness. Happily these comments do not apply to the many medical schools which, in varying degree, have had the vision to recognize what they may contribute to the health of the nation, bound in principle by certain of the stipulations of the Hippocratic Oath of the individual practitioner.

25 YEARS AGO

Present Status of Treatment of Pulmonary Tuberculosis.*

"The marked decrease in the mortality of pulmonary tuberculosis is undoubtedly due to many causes. It is not, many hold, a true measure of the decrease of the morbidity of the disease. Pulmonary tuberculosis is still a very menacing cause of death to both sexes during the period of greatest bodily and mental activity. The keen desire for a cure for tuberculosis, a true therapia magna sterilisans, so widely spread at the beginning of the century, is now less evident. Some foundations and laboratories consider tuberculosis an unpromising field of endeavor and have left it largely to the clinicians and sanitarians, who have contributed much....

"To assess the value of different methods of treatment in any chronic disease is far from simple. The faith of him who introduces a new measure is too often passed on to him who receives it. Several years ago—I attempted to show . . . what a powerful effect suggestion, applied consciously or unconsciously, played in the results of treatment. . . . Misery undoubtedly begets credulity. This is probably the explanation of why many measures for the relief of pulmonary tuberculosis are helpful in the hands that introduce them, failures in the hands of others.

"We hear today on all sides how the treatment of pulmonary tuberculosis has been resolutionized since the introduction of collapse therapy. For the 'far advanced' patient and for many of the progressively 'moderately advanced' patients this is true. We all hail the advances made possible by the fundamental studies not only of the surgeons but also of the physicians....

"The majority of those familiar with pulmonary tuberculosis in all its stages do not hold that patients in the minimal stage require, by and large, any form of surgical treatment. Certainly the great majority have recovered without such interference, and the last word is chosen carefully. The records at the Trudeau Sanatorium reveal only 8 per cent of these 'minimal' patients dead at the end of 15 years. Such patients rarely fall into the hands of the surgeons....

"It is then extremely important to know the proper treatment of this early stage of pulmonary tuberculosis. As soon as it has been diagnosed and as soon as it is determined that the lesion is active, rigorous treatment should be instituted. Now this treatment, less empirical than it was some 35 years ago, still revolves about the triad of rest, food, and air....

"(1). Concerning rest. Injury ever demands rest for repair. . . . The recollection of this slow progress has a very salutary effect upon their future actions. My suggestion is that in proportion as you can give any organ functional rest so you can aid it to recover from tuberculosis.

*Brown, Lawrason: The Present Status of the Treatment of Pulmonary Tuberculosis, Ann. Int. Med. 10:147, 1936.

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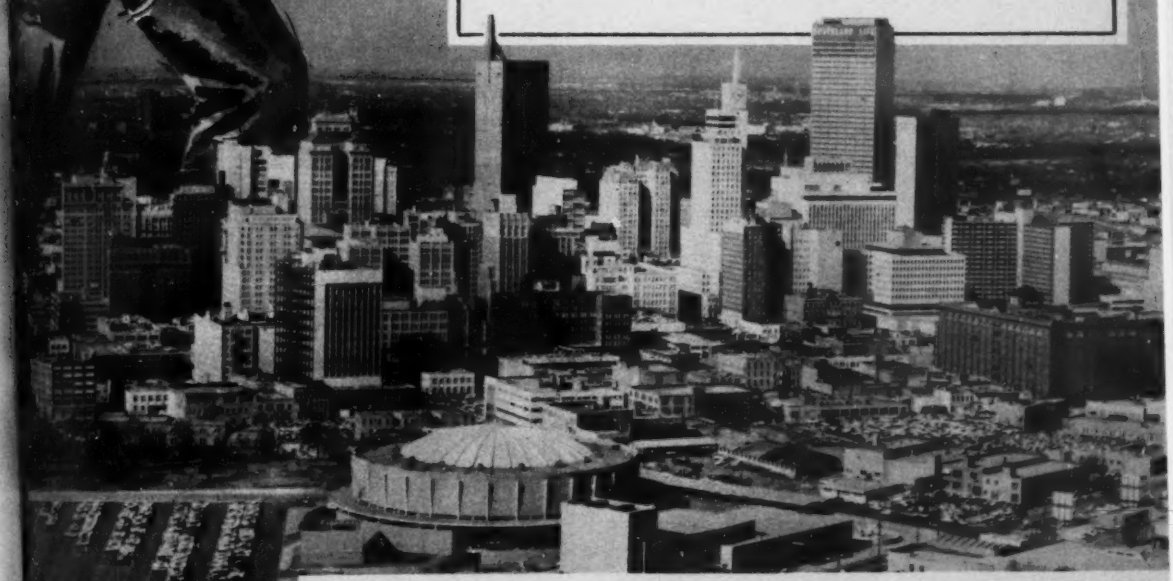

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  Ophthalmology & Otolaryngology
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- Entertainment for the ladies

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"(2). Concerning food. . . . For some years, in the hope of changing an exudative into a proliferative reaction, I have been using, with some encouragement, a diet high in vitamins C and D, restricting the intake of sodium chloride and giving dicalcium phosphate. I would like to suggest that the least amount of food that any patient who is under weight can gain upon is the optimum diet for that patient.

"(3). Concerning fresh air. . . . Today we know that fresh air affects the lungs no more, no less, than it does the knee. The chief effect of aerotherapy is manifested through the skin, and a variation of 20 degrees during the 24 hours is highly desirable. . . . I would suggest that recovery from pulmonary tuberculosis depends upon six or seven hours in the open, and on good ventilation during the remainder of the twenty-four.

"(4). Concerning education. This should begin at the time of diagnosis. Ignorance inflicts often severe and possibly fatal penalties. . . . Three months are necessary for the education of any patient. The time you keep him in bed is your golden opportunity. He is most anxious to learn how to avoid bed in the future. . . .

"For patients in the minimal stage it is remarkable what these apparently simple measures, when intelligently applied, will accomplish. I have already stated that among the patients discharged from the Trudeau Sanatorium it has kept 92% alive for at least 15 years. . . .

"When the patient has passed beyond this early stage the picture changes. The outlook is very different and much more serious, for the progress of the disease may now be difficult to check or such damage may already have taken place that any hope that a permanent arrest may follow the simple measures previously outlined has to be abandoned. . . . This is the stage of disease for which surgical treatment is usually recommended and is often successful. . . . Artificial pneumothorax is, of course, included under this head.

"Finally I would like to emphasize the thought that recovery from pulmonary tuberculosis depends not only upon what we do for the patient but much upon what he brings with him to the physician, in his head as well as in his lungs. We can assist, but do we improve upon the vis medicatrix naturae as brought about by rest, food, air and education?"

ANNOUNCEMENT

Southern Society for Pediatric Research

The Second Annual Meeting of The Southern Society for Pediatric Research will be held in Atlanta, Georgia, November 17-18, 1961. For details as to housing, etc., contact Dr. W. G. THURMAN, Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia.

Deadline for Abstracts (300 words—double spaced) is September 10th, and they should be sent to the above address.

SOUTHERN MEDICAL NEWS

State News Items

During the Southern Medical Association meeting in Dallas this Fall, the University of Pennsylvania School of Medicine alumni will have a reception-buffet dinner at the Adolphus Hotel, November 7. The honored guests will be Dr. Lee F. Turlington, President of SMA, and Mrs. Turlington, and Dr. A. Clayton McCarty, President-Elect of SMA, and Mrs. McCarty. Drs. Turlington and McCarty are both alumni of the University of Pennsylvania. The local chairman is Dr. Stewart A. Fish, Dallas.

The University of Colorado School of Medicine will sponsor a postgraduate course on Hepatic Pathology, Aug. 7-11, 1961. For further information contact the Office of Postgraduate Medical Education, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver 20, Colorado.

ALABAMA

The following Alabama physicians are newly-certified by the American Board of Obstetrics and Gynecology: Dr. Horace G. Bramm, Huntsville; Dr. Homer H. Floyd, Florence; Dr. Sidney S. Frey, Fairfield; and Dr. Frederick B. Jones, Mobile.

New officers of the Alabama Association of Pathologists are: Dr. Robert W. Mowry, Birmingham, President; Dr. Joseph Beaird, Birmingham, Vice-President; and Dr. Earl B. Wert, Mobile, Secretary-Treasurer.

Dr. Harvey B. Searcy, Tuscaloosa, has received that city's Civitan Club award for "Tuscaloosa's Citizen of the Year."

Dr. Seaburt Goodman, Birmingham, has been inducted as a Fellow of the American College of Chest Physicians.

New members of the Jefferson County Medical Society are Drs. John T. Carlin and Ingeborg M. Johnson, both of Birmingham.

Newly-elected officers of the Alabama Orthopaedic Society are: Dr. Charles H. Wilson, Birmingham, President; Dr. Chestley L. Yelton, Birmingham, Vice-President; and Dr. John M. Higginbotham, Birmingham, Secretary-Treasurer.

ARKANSAS

The following Clarksville physicians are officers of the Johnson County Medical Society: Dr. James M. Kolb, President; Dr. R. H. Manley, Vice-President; and Dr. W. R. Scarborough, Secretary. Dr. Kolb has also been re-appointed to the Committee on Medical Practices in the American Medical Association.

Newly-elected officers of the Arkansas Medical Society are: Dr. William A. Snodgrass, Jr., Little Rock, President; Dr. H. King Wade, Jr., Hot Springs, President-Elect; Dr. M. E. Blanton, Jonesboro, First Vice-President; Dr. Charles W. Reid, Pine Bluff, Second Vice-President; Dr. L. E. Drewrey, Camden, Third Vice-President; Dr. H. Elvin Shuffield, Little Rock, Secretary; Dr. W. R. Brooksher, Fort Smith, Secretary Emeritus; and Dr. Ben N. Saltzman, Mountain Home, Treasurer.

Dr. Edward M. Cooper, Jonesboro, is President of the Craighead-Poinsett Medical Society, and Dr. J. H. McCurry, Cash, is lifetime Secretary.

Dr. G. F. Wynne, Warren, has been named President of the Warren Rotary Club.

New members of various county medical societies in Arkansas include: *Craighead-Poinsett,* Dr. James R. Mayfield, Jonesboro; *Garland,* Drs. D. B. Stough III and Shelby S. Gamble, both of Hot Springs; *Greene-Clay,* Dr. Anthony Frank Isele, Piggott; *Lawrence,* Dr. Wayne B. Glenn, Lynn; *Logan,* Dr. B. G. Parker, Booneville; *Miller,* Dr. Mitchell Young, Texarkana; *Phillips,* Dr. Evan James Kurts, Helena, and Dr. Daniel Tonymon, Marvell; *Pulaski,* Drs. Thomas Moore Fletcher, John R. Stotts, David L. Liberman, William B. Riley, Jr., and Ben M. Lincoln, all of Little Rock; *Saline,* Drs. J. L. Martindale and M. Wayne Reynolds, both of Benton; *St. Francis,* Dr. Marvin L. Purifoy, Forrest City; and *Union,* Dr. Henry B. Rogers, El Dorado.

DISTRICT OF COLUMBIA

The International Medical Club of Washington has elected the following officers: Dr. Arthur A. Morris, President; Dr. Donald Stubbs, First Vice-President; Dr. Edgar Copeland, Second Vice-President; Dr. Harry Lee Claud, Third Vice-President; Dr. Robert Choisser, Secretary; Dr. Oscar B. Hunter, Treasurer; and Dr. A. B. Bennett, Historian. Dr. Claud is a Past Chairman of the Council of Southern Medical Association, and Dr. Hunter is currently Councilor from D. C. to SMA.

Brig. General Clinton S. Lyter, MC, USA, has been appointed the new Commanding General of the Walter Reed Army Medical Center.

New members of the Medical Society of the District of Columbia are: Drs. Ross J. Clark, Bernard Drabkin, Charles H. Epps, Jr., John D. Herman, Lydia B. Kronfeld, and Robert E. Lee.

The following physicians are serving as officers of both the Section on Anesthesiology of the Medical Society of the District of Columbia and the D. C. Society of Anesthesiologists: Dr. John Esau, Chairman; Dr. Clarence L. Hebert, Vice-Chairman; and Dr. Ervin N. Chapman, Secretary-Treasurer.

Officers of the District of Columbia Trudeau Society are: Dr. Milton Gusack, President; Dr. Moe Weiss, President-Elect; Dr. Joseph H. Matthews, Vice-President; and Dr. William J. Washington, Secretary-Treasurer.

Dr. George E. Schreiner has been chosen President-Elect of the American Federation for Clinical Research and appointed to the Editorial Board of the *American Journal of Medicine.* Dr. Schreiner is Associate Professor of Medicine of Georgetown University School of Medicine and Director of the Renal and Electrolyte Division.

Dr. Andrew A. Marchetti, Professor and Head of the Department of Obstetrics and Gynecology at Georgetown University School of Medicine, has been elected Director of the American Board of Obstetrics and Gynecology.

Dr. Henry Amiss Hornthal is President of the Greater Washington Area Alumni Association of the Medical College of Virginia.

New Fellows of the American Academy of Pediatrics include Drs. Walter A. Combs and Harold M. Hobart.

Drs. William T. Gibb and Austin R. Rohrbaugh, Jr., have been re-elected to the Board of Trustees of the Suburban Hospital Association.

FLORIDA

The following Florida physicians have been certified by the American Board of Obstetrics and Gynecology: Capt. Robert W. Baker, Orlando AFB; Dr. James S. Bates, Jr., Hollywood; Dr. Duane C. Deen, Winter Park; Dr. Charles M. Garland, Jr., Key West; Dr. Hugh M. Hill, Gainesville; Dr. Frank G. Long, Jacksonville; Dr. Albert B. McCreary, St. Petersburg; Dr. Donald McMahon, Jr., Pensacola; Dr. James P. McNeil, Jr., Jacksonville; Dr. John G. Maclure, North Miami; Dr. Richard M. Mann, Miami Beach; Dr. Clifford B. Miles, Pompano Beach; Dr. Laurent V. Radkins, Ft. Myers; Dr. Warren V. Stough, Ft. Lauderdale; Dr. Jean B. Williams, Jr., Jacksonville; Dr. Samuel B. Witten, Jacksonville; and Dr. Henry L. Wright, Tampa.

Dr. Shaler Richardson, Jacksonville, has received the Certificate of Merit from the Florida Medical Association, its highest honor. Dr. Richardson served as Editor of the *Journal* of the Florida Medical Association for 33 years and is now Editor Emeritus.

Dr. Edward R. Annis, Miami, has been appointed Editor-at-large of the magazine *Medical Economics.*

Dr. Ruth Boynton, Coral Gables, is Secretary-Treasurer of the American College Health Association.

Dr. Samuel C. Harvard, Brooksville, is President of the Florida Medical Association.

Dr. Henry I. Langston, Apalachicola, has been named President-Elect of the Florida Association of County Health Officers. He is director of the health units in Franklin, Gulf and Wakulla Counties.

Dr. Leon S. Eisenman, Hialeah, has been elected President of the Hialeah Industrial Lions Club for 1961-62.

GEORGIA

Dr. Donald S. Bickers, Atlanta, is now serving on the Executive Committee of the Congress of Neurological Surgeons.

Continued on page 935

BOOKS RECEIVED

Radiopaque Diagnostic Agents. By Peter K. Knoefel, M.D., Professor of Pharmacology, University of Louisville, Kentucky. 139 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $6.75.

Strangulation Obstruction. By Isidore Cohn, Jr., M.D., Professor of Surgery, Louisiana State University School of Medicine. American Lecture Series. 259 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $11.75.

Management of Hypertensive Diseases. By Joseph C. Edwards, M.D., Assistant Professor of Clinical Medicine, Washington University School of Medicine, St. Louis. 420 pages. St. Louis: The C. V. Mosby Company, 1960. Price $15.00.

Diagnosis of Upper Gastrointestinal Hemorrhage. By Eddy D. Palmer, M.D., Clinical Associate Professor of Medicine, Baylor University College of Medicine, Houston, Texas. American Lecture Series. 63 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $4.75.

Prosthetic Valves for Cardiac Surgery. By Editor-in-Chief K. Alvin Merendino, M.D., Department of Surgery, University of Washington, School of Medicine, with Associate Editors Andrew G. Morrow, M.D., C. Walton Lillehei, M.D., and William H. Muller, Jr., M.D. 586 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $8.25.

Clinical Psychiatry. By W. Mayer-Gross, M.D., F.R.C.P., Senior Fellow in the Department of Experimental Psychiatry, Medical School, University of Birmingham; Eliot Slater, M.A., M.D., F.R.C.P., D.P.M., Physician in Psychological Medicine, The National Hospital, London; and Martin Roth, M.D., F.R.C.P., D.P.M., Professor of Psychological Medicine, King's College, University of Durham. 657 pages. Baltimore: The Williams & Wilkins Company, 1960. Price $13.00.

Pathology. A Dynamic Introduction to Medicine and Surgery. By Thomas M. Peery, M.D., and Frank N. Miller, Jr., M.D., Associate Professor of Pathology, The George Washington University School of Medicine, Washington, D. C. 598 pages. Boston: Little, Brown & Company, 1961. Price $5.50.

Tobacco. Experimental and Clinical Studies. By P. S. Larson, Ph.D., Professor of Pharmacology; H. B. Haag, M.D., Professor of Pharmacology; and H. Silvette, Ph.D., Visiting Professor of Pharmacology, Medical College of Virginia, Richmond. 921 pages. Baltimore: The Williams & Wilkins Company, 1961. Price $20.00.

Surgical Diseases of the Lung. By Buford H. Burch, M.D., Chief of Thoracic Surgery, Chest Center, Patton State Hospital, Calif.; and Arthur C. Miller, M.D., Assistant Professor, Division of Surgery, College of Medical Evangelists, Loma Linda, Calif. 128 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $8.50.

Systemic Lupus Erythematosus. By Daniel L. Larson, M.D., Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons. 205 pages. Boston: Little, Brown & Company, 1961. Price $7.50.

Medical Forms and Procedures for Industry. By Herbert L. Herschensohn, M.D., Associate Clinical Professor of Industrial Medicine and of Preventive Medicine and Public Health, University of California at Los Angeles. 187 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $8.50.

The Management of Pediatric Practice. By Hugh C. Thomason, M.D., and Joseph B. Seagle, M.D., Department of Pediatrics, Tucson Clinic, Tucson, Arizona. 172 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $7.50.

The Inorganic Ion Content of the Cell. Ciba Foundation Study Group Number 5. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. 96 pages. Boston: Little, Brown & Company, 1961.

Multiple-Choice Examinations in Medicine. A Guide for Examiner and Examinee. By John P. Hubbard, Professor of Public Health and Preventive Medicine, University of Pennsylvania School of Medicine; and William V. Clemans, Ph.D., Director of Testing Services, National Board of Medical Examiners. 180 pages. Philadelphia: Lea & Febiger, 1961. Price $3.75.

Outline of Fractures. By John Crawford Adams, M.D., F.R.C.S. (England), Consultant Orthopaedic Surgeon, St. Mary's Hospital, London, and St. Vincent's Orthopaedic Hospital, Pinner. Third Edition, 258 pages. Baltimore: The Williams & Wilkins Company, 1960. Price $6.50.

Cancer of the Rectum. Volume III of *Neoplastic Disease at Various Sites.* Edited by Cuthbert E. Dukes, O.B.E., M.D., M.Sc., F.R.C.S., Consulting Pathologist, St. Mark's Hospital, London. 295 pages. Baltimore: Williams & Wilkins Company, 1960. Price $10.00.

Textbook of Physiology. By W. W. Tuttle, Ph.D., Sc.D., Professor Emeritus of Physiology, and Byron A. Schottelius, Ph.D., Associate Professor of Physiology, both of the College of Medicine, State University of Iowa. Fourteenth Edition. 521 pages, 313 illustrations. St. Louis: The C. V. Mosby Company, 1961. Price $7.00.

Recent Advances in Tropical Medicine. By Sir Neil Hamilton Fairley, K.B.E., F.R.C.P., M.D.(Lond.), Consulting Physician, Hospital for Tropical Diseases, London; A. W. Woodruff, M.D. (Durh.), Ph.D. (Lond.), Wellcome Professor of Clinical Tropical Medicine; and J. H. Walters, M.D. (Camb.), F.R.C.P., Physician, Hospital for Tropical Diseases, London. Third Edition. 466 pages, 15 illustrations. Boston: Little, Brown & Company, 1961. Price $11.00.

A Handbook of Differential Oral Diagnosis. By Major M. Ash, Jr., D.D.S., Associate Professor of Oral Pathology and Periodontia, The University of Michigan School of Dentistry, Ann Arbor. 219 pages. St. Louis: The C. V. Mosby Company, 1961. Price $6.50.

Specifications for Pesticides. World Health Organization. 523 pages. New York: Columbia University Press, 1961. Price $10.00.

The Physics of Radiology. By Harold Elford Johns, M.A., Ph.D., F.R.C.S., L.L.D., Professor of Physics and Professor of Medical Biophysics, University of Toronto. Second Edition. 747 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $23.00.

Multiple Sclerosis. Prognosis and Treatment. By Leo Alexander, M.D., Director Multiple Sclerosis Research Clinic and Neurologic Unit, Division of Psychiatric Research, Boston State Hospital; Austin W. Berkeley, Ph.D., Professor of Psychology, Boston University; and Alene M. Alexander, Multiple Sclerosis Research Clinic, Boston State Hospital. American Lecture Series. 163 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $7.50.

Surgery of the Acute Abdomen. By John A. Shepherd, V.R.D., M.D., Ch.M.(St. And.), F.R.C.S.Ed., F.R.C.S., Eng., Q.H.S., Consultant General Surgeon, Liverpool. 1,210 pages. Baltimore: The Williams & Wilkins Company, 1961. Price $18.50.

Surgical Treatment of Trauma. Edited by Preston A. Wade, M.D., with 35 contributors. 760 pages. New York: Grune & Stratton, Inc., 1960. Price $26.50.

The Social Epidemiology of Mental Disorders. By E. Gartly Jaco, Cleveland Psychiatric Institute and Western Reserve University. 217 pages. New York: Russell Sage Foundation, 1960. Price $3.50.

Welfare in America. By Vaughn Davis Bornet, Ph.D. 311 pages. Norman, Okla.: University of Oklahoma Press, 1960. Price $4.95.

Bedside Medicine. By I. Snapper, M.D., Director of Medicine and Medical Education, Beth-El Hospital, Brooklyn, N. Y. 561 pages. New York: Grune & Stratton, Inc., 1960. Price $14.50.

Clinical Gastroenterology. By F. Avery Jones, M.D. (Lond.), F.R.C.P. (Lond.), Physician, Central Middlesex Hospital; and J. W. P. Gummer, M.S. (Lond.), F.R.C.S. (Eng.) Surgeon, Central Middlesex Hospital. 632 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960. Price $15.50.

The Central Nervous System and Behavior. Transactions of Third Conference, February 1960. Edited by Mary A. B. Brazier, D.Sc., Neurophysiological Laboratory, Massachusetts General Hospital. 461 pages. New York: Josiah Macy, Jr., Foundation, 1960. Price $7.50.

Dunham's Premature Infants. By William A. Silverman, M.D., Associate Professor of Clinical Pediatrics, College of Physicians and Surgeons, New York. Third Edition. 558 pages. New York: Paul B. Hoeber, Inc., 1961. Price $15.00.

Pioneer Microbiologists of America. By Paul F. Clark, Emeritus Professor of Medical Microbiology, the University of Wisconsin. 355 pages. Madison, Wis.: The University of Wisconsin Press, 1961. Price $6.00.

BOOK REVIEWS

Clinical Flame Photometry

By Henry A. Teloh, M.D., Assistant Professor of Pathology, Northwestern University Medical School. 93 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $4.50.

This volume should be useful to the pathologist, medical technologist, clinical chemist, and others dealing with the clinical application of flame photometry. The author's style is lucid and direct. Much of the value to be derived from this book is in the chapters dealing with pertinent background information including a historical review of the subject, and discussions of the theory of emission spectrophotometry instrument design, inference effects, and precautions in flame photometry technic. There are also chapters dealing with the quantitation of cations including sodium, potassium, calcium and magnesium. Since the author used the Beckman Model B Spectophotometer with flame attachment in obtaining his data, those workers using other instruments will have to adapt the methodology presented according to their own needs. The bibliography includes approximately 70 references to the literature.

Clinical Gastroenterology

By F. Avery Jones, M.D. (Lond.), F.R.C.P. (Lond.), Physician, Central Middlesex Hospital; and J.W.P. Gummer, M.S. (Lond.), F.R.C.S. (Eng.), Surgeon, Central Middlesex Hospital. 632 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960. Price $15.50.

This compact text is clinically oriented toward the diagnosis and treatment of gastrointestinal disorders with regard to the practitioner. It does not cover diseases of the liver nor biliary tract, nor does it discuss the problems of proctology, *per se*. While it does not purport to be comprehensive, it is an excellent selective study based on an extensive clinical experience and research background by the gastroenterology group at the Central Middlesex Hospital in London. Its introduction is a well-conceived chapter on the interpretation of symptoms related to disorders of the alimentary tract and from this it proceeds through 20 chapters commenting on most of the pertinent gastrointestinal maladies in a lucid and interesting fashion.

Although clinically oriented, the pathologic and pathophysiologic aberrations are frequently discussed and reference material is available at the end of each chapter. There is an excellent assortment of pertinent illustrations.

The final chapter on diagnostic technics will be of considerable use to the practicing physicians who supplement it with the references provided.

Representing, as it does, primarily the experience and philosophy of a single group it will suffer the criticism that certain opinions are treated as facts with inadequate discussion of other possible explanations for symptoms or rational for treatment. Nevertheless, this is a well-written and pleasantly personal text based on the broad clinical experience of one of the world's leading gastroenterological centers. It may find a place in the library of anyone maintaining an interest in gastrointestinal disease.

Instructional Course Lectures, Vol. XVII, 1960

Edited by Fred C. Reynolds, M.D., St. Louis. 406 pages, illustrated. St. Louis: The C. V. Mosby Company, 1960. Price $18.50.

Each year at the meeting of the American Academy of Orthopaedic Surgeons a large number of instructional courses is presented. Each of these courses represents a carefully prepared presentation by an authority in his field. The committee on the Instructional Course Program under the direction of Dr. Fred C. Reynolds has brought together the new courses which were presented in the 1960 meeting of this organization. The major subjects covered include fractures, bone graft surgery, children's orthopedics, athletic injuries, and disability evaluation. A new section has also been added on surgical approaches to the cervical spine.

This volume constitutes another addition to what is probably the best current text of orthopedic concepts and procedures.

It is highly recommended that all those who are attempting to keep abreast of orthopedic matters not only obtain this volume but plan to obtain the others as they appear.

It is particularly important to note that the editor and his committee now make this material available while it is current information, and the time delay between the meeting of the organization and the availability of the volume is being shortened each year.

Gynecological Urology

Edited by Abdel Fattah Youssef, M.B., D.S., D.G.O., M.Ch., F.I.C.S., Lecturer in Obstetrics and Gynecology, Cairo University. 826 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960. Price $22.50.

This new comprehensive work on *Gynecological Urology* was compiled and edited by Abdel Fattah Youssef, an international known lecturer in Obstetrics and Gynecology at Cairo University, Egypt. Despite the close relationship between diseases of the female genital and urinary systems advances in the fields of urology and gynecology have run separate, parallel courses, few persons claiming to be experts in both specialties. In the introductory chapter by Houston Everett, he cites *Diseases of the Kidneys, Ureters and Bladder* by Kelly and Burnham (1914) as the first extensive work devoted to urology in female patients. Several subsequent references are mentioned, the last of which was by Everett entitled *Gynecological and Obstetrical Urology* (1944 and 1947). During the intervening time many papers have been written and manuals on surgical technic with special reference to bladder surgery. However, *Gynecological Urology* by Yous-

sef takes the "big step forward" with an attempt to consolidate in book form modern advances in this overlapping "no man's land" between specialties utilizing the experience of 31 eminent men from 8 countries. To mention just American contributors: T. C. Bramhall, M. F. Campbell, V. S. Counseller, H. J. Davis, H. S. Everett, J. P. Greenhill, A. H. Kegel, L. E. McCrea, J. V. Meigs and J. S. Welch. These and many more internationally known men take part in this exciting new book. If one doubts the experience of other contributors consider a statement made by Naguib Mahfouz of Cairo University: "In over ONE THOUSAND operations which I performed for different types and varieties of urinary fistulae, I was able to tackle the fistulae by the vaginal route in 99% of the cases." This is only a sample of the wealth of information one will find in this book. Written primarily for the specialist it includes detailed discussions of all aspects of gynecological urology with special orientation toward surgical technic in clear, concise manner with adequate diagrams and illustrations. This book undoubtedly will be widely accepted and assume a well-earned position in the personal library of the gynecologist.

Traumatic Lesions of Peripheral Vessels

By Carl W. Hughes, M.D., Lt. Col., Medical Corps, U. S. Army, Assistant Chief, Department of Surgery and Chief, General Surgery Service, Tripler U. S. Army Hospital, and Warner F. Bowers, M.D., Col., Medical Corps, Chief, Department of Surgery, Tripler U. S. Army Hospital. 191 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1961. Price $8.00.

This is a well-documented, profusely illustrated and thoroughly comprehensive monograph written by two experienced military surgeons. The entire story of the development of the most modern concepts in the management of peripheral vascular injuries is narrated, pointing up the deficiencies and inconsistencies of each of the older methods. The authors discuss the relative merits of the various types of autografts, homografts and synthetic prostheses. There is a separate chapter for the detailed management of acute vascular injuries, A-V fistulae, and traumatic aneurysms. Especially valuable for the surgeon is a chapter summarizing the various anatomical approaches to both the major and the minor arterial branches. An exhaustive bibliography is included as well as many clinical photographs and radiophotographs of fine quality.

The Surgery of Mitral Stenosis

By Robert P. Glover, M.D., Assistant Clinical Professor of Surgery, and Julio C. Davila, M.D., Instructor in Surgery, both of University of Pennsylvania School of Medicine. 210 pages. New York: Grune & Stratton, Inc., 1961. Price $9.50.

This is a comprehensive monograph by two competent authorities in the field of acquired heart disease. Chapter headings include the anatomy and physiology of the mitral valve, the hemodynamic changes in mitral valve disease, the evaluation of patients for surgery and preoperative and postoperative care. The methods described are those which have been used in many hundreds of cases under the authors' personal supervision. Valuable comments are included on the handling of the different types of the heavily calcified leaflets. The surgical pitfalls are discussed with the familiarity achieved only with vast experience in the varied manifestations of the disease. The problem of mitral regurgitation and associated aortic lesions are also dealt with. The authors provide an exhaustive list of references dealing with all aspects of the physiology and the surgical management of mitral stenosis, mitral insufficiency, and aortic stenosis.

Chemistry of Pancreatic Diseases

By Harris Busch, M.D., Associate Professor of Pharmacology, University of Illinois College of Medicine. American Lecture Series. 160 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $5.25.

This monograph, written by a pharmacologist, is a succinct effort to summarize the present knowledge of the biochemistry of the pancreatic secretions. The text is divided into three parts in which the chemistry of the exocrine diseases, the endocrine diseases and neoplasia of the pancreas are considered. The author succeeds in simplifying and condensing a very complex field but the clinical information is superficial and not directed particularly at clinicians. The bibliography is quite adequate. The book would be a fine starting point for those interested in developing a biochemical background in pancreatic disease.

Epilepsy and Related Disorders

By William G. Lennox, M.D., Associate Professor of Neurology, Emeritus, of Harvard University; and Margaret Lennox, M.D., Institute of Neurophysiology, Copenhagen. Two volumes, 1,145 pages. Boston: Little, Brown & Company, 1960. Price $13.50.

In these two volumes, the late Dr. William Lennox, with the collaboration of his daughter, attempts "a broad portrayal of diverse manifestations, causes, consequence and treatments" relating to epilepsy. The historical aspects of this disorder and the problems of the individual patient, both medical and social, are also considered.

In the first volume, after an introduction to the general subject of paroxysmal disorders, the historical perspective, classification and detailed description of the protean epileptic manifestations followed by the statistical background and the genetic considerations are skillfully and attractively presented. The wealth of clinical material which was at the disposal of the senior author is used to illustrate the text.

In volume two the general subject of "acquired" or "symptomatic" epilepsy is treated at length. This is followed by sections on the mentality and personality of patients with epilepsy, a review of the neurophysiologic, neuroanatomic and neurochemical investigations relating to the management of this disorder. In addition to a thorough description of drug therapy, the many problems besetting the epileptic as he attempts to secure an education and lead an active family life are all discussed in a wise and cogent manner. The laws regarding marriage, sterilization, driving an automobile and other broad matters of concern to patients and those who would help them are described lucidly and frankly.

These volumes will remain a fitting monument to the memory of a good and kind physician who con-

ducted for many years a one man crusade to extend our understanding of this disease and the problems of its victims. These two volumes deserve a place in the library of all neurologists and other physicians interested in epilepsy and related disorders.

There is an extensive bibliography of almost 800 references as well as a list of 346 relevant books. The volumes are attractively printed and bound and reflect credit upon the publisher. As the result of an anonymous philanthropy, these books are offered at a modest price.

Work and the Heart

Edited by Francis F. Rosenbaum, M.D., Associate Clinical Professor of Medicine, and Elston L. Belknap, M.D., Professor and Director, Department of Occupational and Environmental Medicine, both of Marquette University School of Medicine. 521 pages. New York: Paul B. Hoeber, Inc., 1959. Price $12.00.

The entire field of work and its relationship to heart disease is included in this excellent volume. The range of subjects is broad and the coverage is intense. Seventy-four authors have contributed to the contents of a book which is divided into 5 major sections. These are: Basic Physiology, Clinical Physiology, Pathology, Work Classification, and Workmen's Compensation. The results of Cardiac Work Evaluation Clinics are presented, and figures for energy expenditure are included. The latter can be of inestimable value to the clinician who must be involved almost daily with the field of rehabilitation for the cardiac patient. The book also has value in that it brings together in one volume the diverse subjects listed above. Some of the 57 chapters, such as ones on myocardial infarction in garment workers, or heart disease in Indiana farmers, lack general interest. Most of the chapters, however, provide excellent reference sources for timely subjects, covering a broad range of subjects of interest to the practicing cardiologist who is oriented toward basic research as well as the research and practical aspects of the field of rehabilitation of the patient who has heart disease.

French's Index of Differential Diagnosis

Edited by Arthur H. Douthwaite, M.D., F.R.C.P., Senior Physician, Guy's Hospital. Eighth edition. 958 pages, 774 illustrations. Baltimore: The Williams & Wilkins Company, 1960. Price $24.00.

The usefulness of this established reference work is implicit in the appearance of still another edition, in a course thus far of 48 years. The intricately cross-referenced index of 150 pages continues to be a boon to the confused as well as the curious. Although the approach to a problem cannot be based on random reading, it may be quite fruitful to have available concise diagnostic clues to accentuated heart sounds, or bullae, or whatever.

Comparison with an edition of over 30 years ago provides an interesting view of the passage of time. Ataxy has become ataxia, cardiac bruits have become murmurs, skodiac resonance is no longer listed and erythema is now discussed in 1½ pages instead of eight. "Noises in the head" are now graced under "tinnitus," anemia now covers 51 pages rather than 26, blood pressure abnormalities are given 9 pages rather than 2, and aldosteronism, hirsutism and gynecomastia may now be found. Extensive temperature charts are still delightfully in evidence. Colored photographs have replaced many watercolors of old, but equally many remain; without exception the colored prints were reproduced better in the 1928 edition than in the present. On page 62, the original figure and caption have been curiously preserved, illustrating "pseudoleukaemica infantum (von Jaksch's disease)." Perhaps the lack of specificity of splenomegaly, anemia and left shift in infants is a sufficiently useful teaching point to permit the perpetuation of this historic designation of a mistaken entity. Harder to accept is the continuation, in Figures 535 through 540, of nonspecific papillitis, "scrotal" tongue and "geographic" tongue (all totally benign) under the label of "chronic streptococcal glossitis," an entity without justification.

The organization of the book is unchanged, and sizable areas of material are much the same. Far from being archaic, it is mute commentary to the relative amount of factual knowledge that has accumulated. Emphasis may shift and methodology improve to bury old concepts as new ones arise, but manifestations of disease—no matter how susceptible to further study of underlying mechanism—descriptively change but little. Therapy, abnormal physiology and unusual laboratory values are not dwelt upon but rather a thorough collection of signs and symptoms is assembled with their various diagnostic possibilities. The extensive and colorful illustrations coupled with the inordinately large amount of information available and omnipotence of its index continue to recommend this venerable but timeless volume to the student and practitioner, for interest as well as use.

Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment

By H. J. Parish, M.D., F.R.C.P.E., D.P.H., Clinical Research Director, Wellcome Foundation, and D. A. Cannon, O.B.E., M.D., B.Sc., D.T.M. & H. Fifth edition. 279 pages. Baltimore: The Williams & Wilkins Company, 1961. Price $8.50.

The fifth edition in 13 years of this welcome little monograph brings it quite up to date for its avowed purpose of presenting "in convenient form the essential principals of immunology and their practical application in human medicine." The first 4 chapters summarize basic principles and procedures, the next 5 present complete information on antisera, and the bulk of the book of 14 chapters deals with active immunization against infectious disease. The last 5 chapters assemble suggested immunization schedules, comments on personal health records, and a superior chronological history of the development of immunological procedures.

Frequent references are incorporated in the running text, many of them as recent as 1960. Where pertinent, a pleasantly dubious tone is adopted, as in the value of antitoxin in established gas gangrene, or of hyperimmune gamma globulin in mumps exposure. The material spans all commercially available immunologic material, from yellow fever vaccine to BCG, and from staphylococcus "vaccoid" to erysipiloid antiserum. The completeness, authority and practicality of this book are highly commended to all.

MEDICAL NEWS

Continued from page 930

Officers of the Georgia Society of Ophthalmology and Otolarygology include: Dr. C. W. Whitworth, Gainesville, President; Dr. P. Thomas Manchester, Atlanta, Vice-President; and Dr. James T. King, Atlanta, Secretary.

Dr. Frank Robbins, Vidalia, has accepted the position of consulting surgeon on the staff of the Candler County Hospital.

Dr. Robert A. Collins, Jr., Americus, and Dr. Calvin L. Edwards, Dalton, have been inducted as new Fellows of the American College of Surgeons.

The Camden-Charlton Medical Society has recently been granted a charter by the Medical Association of Georgia. Members of the Society are: Dr. J. O. Simmons, Woodbine; Drs. G. W. Barker and Rex Stubbs, St. Marys; Drs. R. D. McCollum and H. H. Robinson, Kingsland; and Drs. J. Jackson, C. H. Harvey, and E. C. Lundell, Folkston.

Dr. Harry E. Rollings, Savannah, has recently been appointed as a Lieutenant Colonel in the Georgia Air National Guard and the USAF Reserve.

Dr. Ulrich H. Harte, Newnan, has been elected a member of the American Society of Abdominal Surgeons.

Recently certified by the American Board of Obstetrics and Gynecology were the following Georgia physicians: Dr. Darnell L. Brawner, Savannah; Dr. Hugh H. Cook, Jr., Ft. Benning; Dr. Jacob Epstein, Atlanta; Dr. F. N. Harrison, Augusta; Dr. Barton A. McCrum, Gainesville; and Drs. Christian R. Moorhead and John D. Thompson, both of Atlanta.

New officers of the Medical Association of Georgia are: Dr. Fred H. Simonton, Chickamauga, President; Dr. Thomas W. Goodwin, Augusta, President-Elect; Dr. Linton Bishop, Atlanta, First Vice-President; and Dr. Lee Battle, Rome, Second Vice-President.

The Georgia GP of the Year is Dr. J. W. Palmer, Ailey.

Dr. Robert L. Brown, Atlanta, is President of the American Radium Society.

KENTUCKY

Officers of the Kentucky Academy of General Practice are: Dr. Edward B. Morgan, Louisville, President; Dr. J. Sankey Williams, Nicholasville, President-Elect; Dr. Robert Sirkle, Lexington, Secretary; and Dr. Roy G. Wilson, Campbellsville, Treasurer.

Dr. Clyde Sparks, Ashland, is President of the Kentucky Surgical Society. Dr. David Kinnaird, Louisville, is Vice-President, and Dr. C. Melvin Bernhardt, Louisville, is Secretary-Treasurer.

Dr. Robert W. Robertson, Paducah, has been appointed to succeed himself for a four year term as a member of the Kentucky State Board of Health. Dr. Branham B. Baughman, Frankfort, has been appointed for a four year term also.

New members of the Kentucky State Medical Association include: Dr. Robert C. Burkhart, Harlan; Drs. William D. Bushong, R. Glenn Greene, and William G. Ward, all of Owensboro; Drs. Herbert P. Hargett, David W. Scott, and Richard C. Turrell, all of Louisville; Dr. Thomas L. Heavern, Jr., Newport; Dr. Richard Holt, Franklin; Dr. Thomas C. Lane, Fulton; Dr. F. R. Larsen, Earlington; Dr. Jesse Page, Mayfield; Dr. Edward F. Slothour, Red Bird; Drs. W. B. Stewart, W. O. West, and J. G. Wilhite, all of Lexington; Drs. Elvis R. Thompson and Marguerite E. Thompson, both of Stone; Dr. D. N. Tweeddale, Madisonville; and Dr. James L. Wagstaff, Fort Thomas.

LOUISIANA

New officers of the Louisiana State Medical Society are: Dr. Ralph H. Riggs, Shreveport, President-Elect; Dr. J. Theo Brierre, New Orleans, First Vice-President; Dr. Gordon W. Peek, Baton Rouge, Second Vice-President; and Dr. Eugene H. Countiss, New Orleans, Third Vice-President.

Recently certified by the American Board of Obstetrics and Gynecology were the following Louisiana physicians: Dr. James C. Atkinson, Baton Rouge; Drs. Herman R. Cohen, Theodore K. Dampeer, Jr., Milton J. Hoffman, and Herman D. Webster, Jr., all of New Orleans; Drs. Joseph P. Martinez III and Gerald E. Posner, both of Opelousas; and Dr. Armant C. Touchy, Metairie.

MARYLAND

Dr. John G. Ball, Bethesda, is the newly-elected Vice-President of the Medical and Chirurgical Faculty of Maryland.

Dr. Abraham J. Mirkin, Cumberland, is President of the Tri-State Area County United Fund Foundation.

MISSISSIPPI

The Fellows of the State Surgical Division of the United States Section, International College of Surgeons, have organized a Mississippi Section of ICS. Dr. J. P. Culpepper, Jr., Hattiesburg, a Past President of Southern Medical Association, is President. Other officers include Dr. Murdock Snelling Handsboro, President-Elect; Dr. Grady Cook, Hattiesburg, Vice-President; and Dr. Willis Walker, Hattiesburg, Secretary-Treasurer.

Dr. J. P. Culpepper III, Hattiesburg, now a hospital fellow (resident) in general surgery at Alton Ochsner Medical Foundation in New Orleans, is the Foundation's first American Cancer Society Clinical Fellow in Surgery. Dr. Culpepper is a graduate of Tulane.

New members of the Mississippi State Medical Association are Dr. David Lee Clippinger, Hazlehurst, and Dr. David Owen Cole, Brookhaven.

New officers of the Mississippi State Medical Association include: Dr. Lawrence W. Long, Jackson, President; Dr. C. P. Crenshaw, Collins, President-Elect; Dr. Joseph L. Guyton, Pontotoc, Dr. Tom H. Mitchell, Vicksburg, and Dr. A. T. Tatum, Petal, Vice-Presidents; and Dr. C. G. Sutherland, Jackson, Secretary-Treasurer.

MISSOURI

Recent promotions at Washington University School of Medicine in St. Louis include: to Professor, Dr. Harvey R. Bernard, Surgery; Dr. Sidney Goldring, Neurological Surgery; Dr. Kathleen Smith, Psychiatry; and Dr. Arthur H. Stein, Jr., Orthopedic Surgery. To Assistant Professor, Dr. John W. Berry, Clinical Medi-

cine; Dr. William S. Coxe, Neurological Surgery; and Dr. Harry C. Morgan, Orthopedic Surgery.

The medical staff of Lutheran Hospital in St. Louis has these officers: Dr. Paul M. Parashak, St. Louis, President; Dr. H. V. Hoefer, St. Louis, President-Elect; Dr. Morris Herman, St. Louis, Vice-President; and Dr. Donald T. Behrens, Clayton, Secretary-Treasurer.

Dr. Avery P. Rowlette, Moberly, is President of the Missouri State Surgical Society. Other officers are: Dr. Ralph R. Coffey, Kansas City, President-Elect; and Dr. John A. Growdon, Kansas City, Secretary.

Dr. Grayson Carroll, Professor of Clinical Urology at the St. Louis University School of Medicine and Head of the Department of Urology at St. John's Hospital, is the President-Elect of the American Urological Association. Dr. Carroll is Second Vice-President of Southern Medical Association.

NORTH CAROLINA

Dr. Mac Roy Gasque, Pisgah Forest, has been appointed to the newly-created post of Medical Director of Olin Mathieson Chemical Corporation. He had been Medical Director of Olin's Ecusta and film operations at Pisgah Forest. Dr. Gasque is an Associate Councilor from North Carolina to Southern Medical Association.

Dr. Eben Alexander, Jr., Winston-Salem, is Treasurer of the Harvey Cushing Society.

Dr. George C. Mackie, Wake Forest, has been honored by the Medical Society of the State of North Carolina as its General Practitioner of the Year.

Dr. G. P. Manire, Professor of Bacteriology and Immunology at the University of North Carolina School of Medicine, is President of the Chapel Hill Chapter of the American Association of University Professors.

Dr. S. B. Alexander, Assistant Administrator of the University of North Carolina Division of Health Affairs, has been advanced to fellowship in the American College of Physicians.

Duke University Medical Center has several news items. Dr. Barnes Woodhall, Dean of the School of Medicine, has been appointed Chairman of the Veterans Administration Special Medical Advisory Group. Dr. Keith S. Grimson, Professor of Surgery, has been elected Vice-President of The Society for Vascular Surgery. Dr. Ivan W. Brown, Jr., Professor of Surgery, has been named an alumni member of Phi Beta Kappa.

OKLAHOMA

Newly-elected officers of the Oklahoma State Medical Association are: Dr. Clinton Gallaher, Shawnee, President; Dr. J. Hoyle Carlock, Jr., Ardmore, President-Elect; Dr. Peter E. Russo, Oklahoma City, Vice-President; and Dr. Mark R. Johnson, Oklahoma City, Secretary-Treasurer.

Officers of the Oklahoma Heart Association include: Dr. E. C. Mohler, Ponca City, President-Elect; and Dr. W. N. Weaver, Muskogee, a Vice-President.

Dr. Frank Stuart, Tulsa, is the new President of the Mid-Central Orthopedic Society.

From the University of Oklahoma Medical School comes word that Dr. Phyllis E. Jones, Associate Professor of Dermatology, has been named Chairman of the Department of Dermatology. Faculty appointments made at the School include: Dr. James A. Merrill, full-time Head of the Department of Gynecology and Obstetrics; Dr. T. Glyne Williams, Associate Professor of Psychiatry and of Preventive Medicine and Public Health; Dr. Forrest L. Scharf, Assistant Professor of Pathology; Dr. Samuel E. Dakil, Instructor in Otorhinolaryngology; Dr. Klaus Jensen, Instructor in Medicine; Dr. Earl E. Smith, Jr., Junior Clinical Assistant in Medicine; and Dr. T. A. Kutkam, Research Associate in Pathology.

SOUTH CAROLINA

Officers of the South Carolina Medical Association include: Dr. Charles N. Wyatt, Greenville, President; Dr. H. J. Gressette, Orangeburg, President-Elect; Dr. Wallis D. Cone, Sumter, Vice-President; Dr. Robert Wilson, Charleston, Secretary; and Dr. Howard Stokes, Florence, Treasurer. Dr. Stokes is also Councilor from South Carolina to Southern Medical Association.

The Alumni Association of the Medical College of South Carolina has these new officers: Dr. Henry F. Ross, Greenville, President; Dr. Charles B. Hanna, Spartanburg, Vice-President; and Dr. John May, Bennettsville, President-Elect.

Dr. A. Richard Johnston, St. George, is First Vice-President of the Association of Surgeons of the Southern Railway System.

TENNESSEE

The Tennessee Valley Medical Assembly will hold its ninth annual assembly at the Read House in Chattanooga, Sept. 25 and 26, 1961. American Academy of General Practice members who attend may be granted 11 hours of Category I credit. For further information contact Dr. Joseph W. Graves, Chairman, 109 Medical Arts Building, Chattanooga.

Officers of the Tennessee Pediatric Society are: Dr. Albert M. Jones, Memphis, President; Dr. Pope B. Holliday, Chattanooga, Vice-President; and Dr. William Crook, Jackson, Secretary-Treasurer.

The Middle Tennessee Medical Association has these officers: Dr. John T. Mason, McMinnville, President; and Dr. Arnold Meirowsky, Nashville, Secretary-Treasurer.

Dr. Edward H. Mabry, Memphis, is President of the Tennessee Radiological Society. Other officers include: Dr. M. D. Ingram, Nashville, President-Elect; Dr. James J. Range, Johnson City, Vice-President; and Dr. B. M. Brady, Memphis, Secretary-Treasurer.

Dr. Cecil B. Tucker, Nashville, Director of the Division of Preventable Diseases, Tennessee Department of Public Health, was recently elected President of the Conference of State and Territorial Epidemiologists.

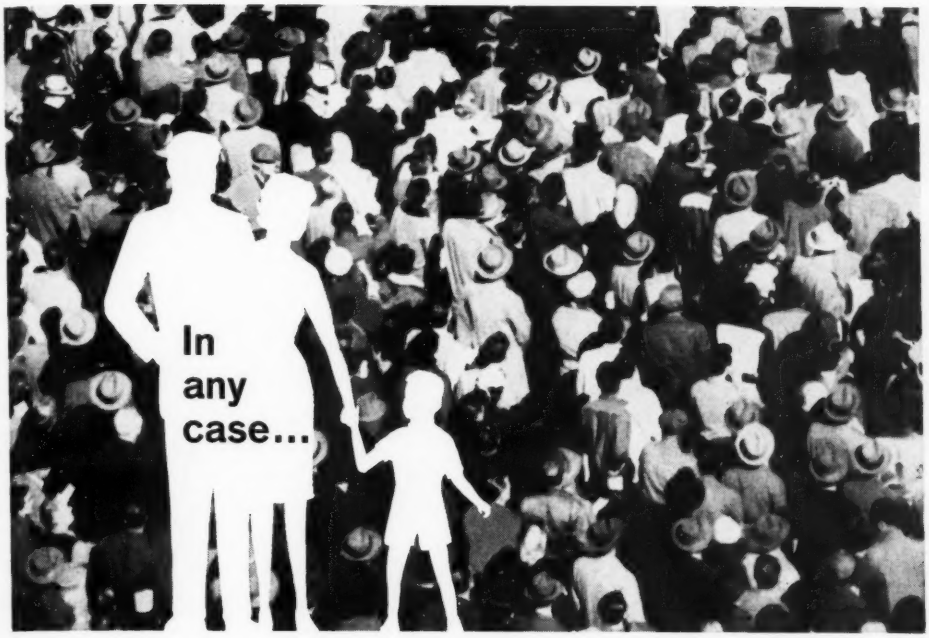
The President of the West Tennessee Heart Association is Dr. Laurence W. Jones, Union City.

Dr. Maurice S. Rawlings, Chattanooga, and Dr. Carl C. Gardner, Jr., Columbia, were elected to Fellowship, and Dr. Robert E. Mabe, Chattanooga, and Dr. Charles L. Neely, Jr., Memphis, to Associateship in the American College of Physicians.

TEXAS

Dr. Titus Harris, Professor and head of the Department of Neurology and Psychiatry at the University of Texas Medical Branch in Galveston, has been elected

Continued on page 50



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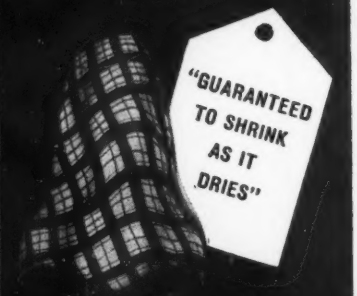

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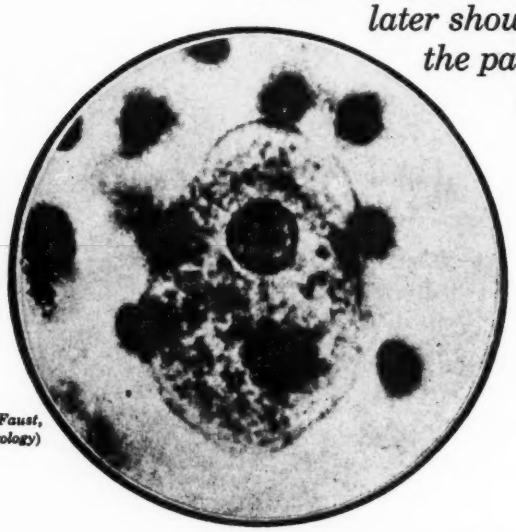

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1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). (To be published in Am. J. Gastroenterol., October, 1960.)

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1. Coolidge, C. W.; Glisson, C. S., Jr., and Smith, A. A.: J. M. A. Georgia 48:167 (Apr.) 1959. 2. Ensey, J. E.: Am. J. Obst. & Gynec. 77:155 (Jan.) 1959. 3. Frech, H. C., and Lanier, L. R., Jr.: J. M. A. Georgia 47:498 (Oct.) 1958.

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Refer to Page 543 — Physicians Desk Reference

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HUMATIN possesses high antibacterial and antiamebic activities, coupled with a low order of oral toxicity.[1] Because it is effective against many gram-negative pathogens, HUMATIN has proved valuable in the treatment of infectious diarrheas and other enteric infections, most of which are caused by bacilli of the gram-negative group.[2-5] Characteristic of the favorable response to HUMATIN is a prompt reduction in the number of stools per day, a decrease in fever, and rapid alleviation of other symptoms of infection.[2,3,5] HUMATIN is also useful in all phases of intestinal amebiasis,[1,5-12] and has shown promise of being useful in the preoperative suppression of intestinal flora,[5] and in the adjunctive management of hepatic coma.[13-15]

HUMATIN is not appreciably absorbed from the gastrointestinal tract and is, therefore, not effective against systemic infections. Systemic toxicity has not been a problem. *See medical brochure for details of administration, precautions, and dosage.*

SUPPLIED: HUMATIN (paromomycin, Parke-Davis) is available as the sulfate in Kapseals,® each containing the equivalent of 250 mg. of base, in bottles of 16.

REFERENCES: (1) Coffey, G. L., *et al.*: *Antibiotics & Chemother.* 9:730, 1959. (2) Courtney, K. O.; Thompson, P. E.; Hodgkinson, R., & Fitzsimmons, J. R.: *Antibiotics Annual* 7:304, 1959-1960. (3) Godenne, G. D.: *ibid.*, 310. (4) McMath, W. F. T., & Hussain, K. K.: *Pub. Health* 73:328, 1959. (5) Personal Communications to Department of Clinical Investigation, Parke, Davis & Company, 1959. (6) Shafei, A. Z.: *Antibiotic Med. & Clin. Therapy* 6:275, 1959. (7) Lopez Elias, F., & Oliver-Gonzalez, J.: *Antibiotic Med. & Clin. Therapy* 6:584, 1959. (8) Carter, C. H.: *Antibiotic Med. & Clin. Therapy* 6:586, 1959. (9) Thompson, P. E., *et al.*: *Antibiotics & Chemother.* 9:618, 1959. (10) Dooner, H. P.: *Antibiotic Med. & Clin. Therapy* 7:486, 1960. (11) Coles, H. M. T., *et al.*: *Lancet* 1:944, 1960. (12) Moffett, H. F., & Toh, S. H.: *Antibiotic Med. & Clin. Therapy* 7:569, 1960. (13) Fast, B. B.; Wolfe, S. J.; Stormont, J. M., & Davidson, C. S.: *Arch. Int. Med.* 101:467, 1958. (14) Mackie, J. E.; Stormont, J. M.; Hollister, R. M., & Davidson, C. S.: *New England J. Med.* 259:1151, 1958. (15) Stormont, J. M.; Mackie, J. E., & Davidson, C. S.: *New England J. Med.* 259:1145, 1958.

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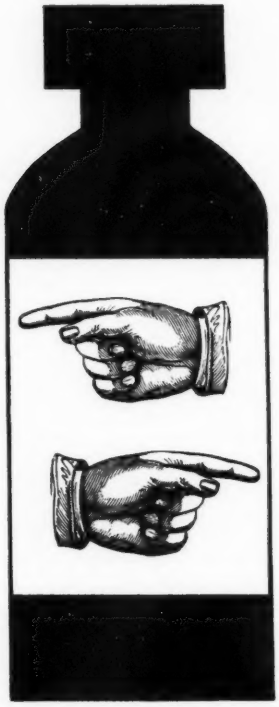

or "drugs anonymous"?

In the field of medicine, as almost everywhere else in a free economy, the trademark concept has evolved over the years. As with most human institutions, there are some who may not consider it ideal; but it has brought about three signal benefits:

To the physician it gives assurance of quality in the drugs he prescribes—assurance backed by the biggest asset of the maker, his reputation.

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2. A new system of generic nomenclature which would magically turn out names not only rememberably simple, but also conforming to the principles of complex chemical terminology.

3. Something new to fill the gap left by the elimination of the trademark incentive to produce new and better drugs.

The American system has been pre-eminent in producing and distributing good medicines. Above all it has been successful in creating new advances in therapy. In a dubious effort to provide cheaper medicines by abolishing the trade names upon which the responsible makers stake their reputations, let us beware of sacrificing this success.

This message is brought to you on behalf of the producers of prescription drugs to help you answer your patients' questions on this current medical topic. For additional information, please write **Pharmaceutical Manufacturers Association,** *1411 K Street, N. W., Washington 5, D.C.*

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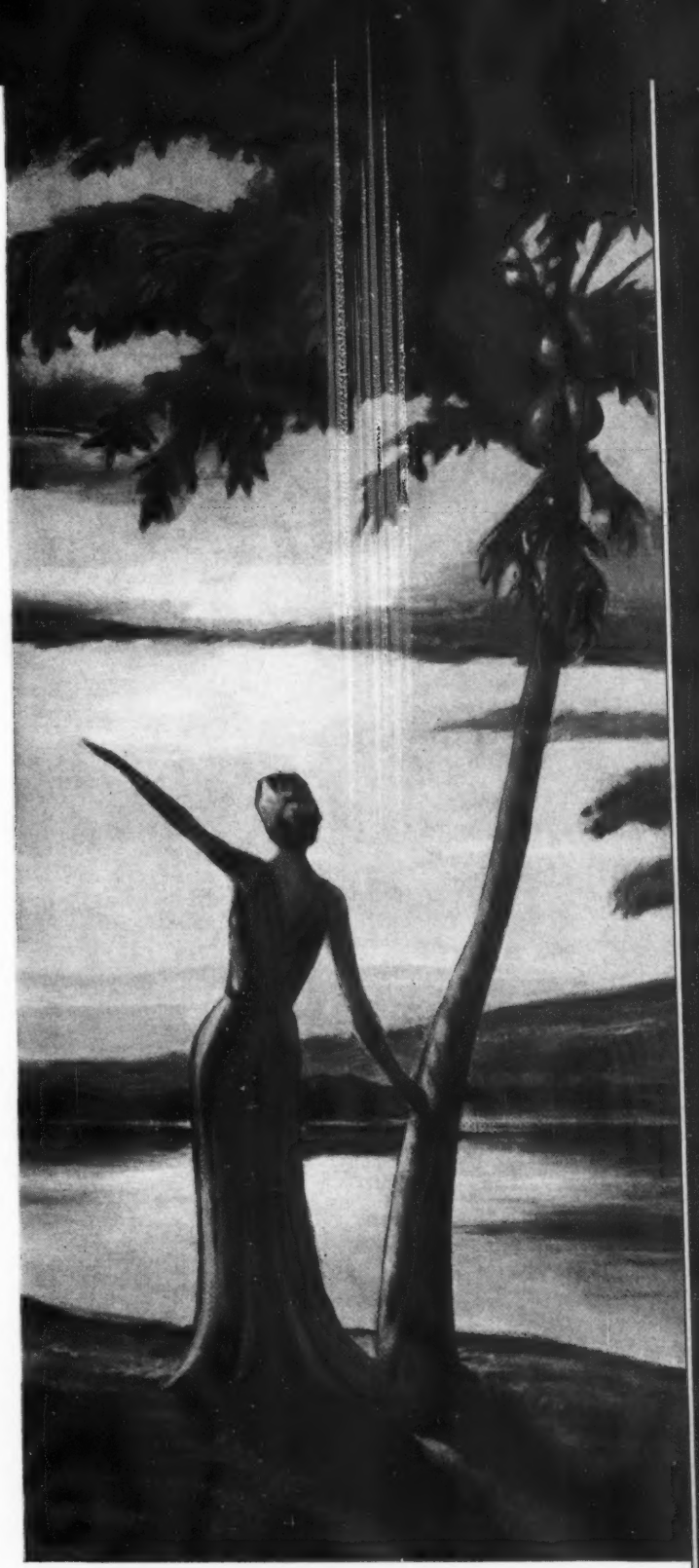
to complete, thorough vaginal cleansing

Meta Cine

mucolytic, acidifying, physiologic vaginal douche



e papain content of Meta Cine is the key ason why it effects such complete cleansing of e vaginal vault. Papain is a *natural* digestant, d is capable of rendering soluble from 200- 0 times its weight of coagulated egg albumin. the vagina, papain serves to dissolve mucus gs and coagulum.

eta Cine also contains lactose—to promote wth of desirable Doderlein bacilli—and thyl salicylate, eucalyptol, menthol and orothymol, to stimulate both circulation and rmal protective vaginal secretions. Meta e's pleasant, deodorizing, *non-medicinal* fra- nce will meet your patients' esthetic demands.

plied in 4 oz. and 8 oz. containers, and in es of 30 individual-dose packets. Dosage: easpoonfuls, or contents of 1 packet, in 2 rts of warm water.

BRAYTEN PHARMACEUTICAL COMPANY *Chattanooga 9, Tennessee*

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Every young couple about to be married needs advice of all sorts, and they'll get it, too – from everybody – some good, some bad. But some of the most valuable counsel they can get – help in planning their own family – comes best from you. Their family happiness for many years can depend on what you suggest to them, including your recommendation for the use of Lanesta Gel.

Lanesta Gel, with or without a diaphragm, is a most effective means of conception control. Lanesta Gel offers faster spermicidal action because it rapidly diffuses into the seminal clot. In fact, Gamble ("Spermicidal Times of Commercial Contraceptive Materials – 1959"*) *found the mean diffusion spermicidal time of Lanesta Gel to be three to seven times faster than the mean diffusion times of ten leading commercially available contraceptive creams, gels, or jellies.*

Lanesta Gel has complete esthetic acceptance and is well tolerated. *Gamble, C. P.: Am. Pract. & Digest. Treat. 11:852 (Oct.) 1960.

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in the wide middle region of pain

Percodan®

Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

TABLETS

fills the gap between mild oral and potent parenteral analgesics[1-7]

- **acts in 5-15 minutes**
- **relief usually lasts 6 hours or longer**
- **toleration excellent... constipation rare**
- **sleep uninterrupted by pain**

Each Percodan* Tablet contains 4.50 mg. dihydrohydroxycodeinone HCl, 0.38 mg. dihydrohydroxycodeinone terephthalate (warning: may be habit-forming), 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

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1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

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For greater flexibility in dosage — Percodan®-Demi: The complete Percodan formula, but with only half the amount of salts of dihydrohydroxycodeinone and homatropine.

1. Blank, P., and Boas, H.: Improved analgesia for moderate pain, Ann. West. Med. & Surg. 6:376, 1952. 2. Bonica, J. J., et al.: The management of postpartum pain with dihydrohydroxycodeinone (Percodan): Evaluation with codeine and placebo, West. J. Surg. 65:84, 1957. 3. Cass, L. J., and Frederick, W. S.: A controlled study in pain relief, M. Times 84:1318, 1956. 4. Chasko, W. J.: Pain-free dental surgery: Postoperative extension of the pain-free state, J. District of Columbia Dent. Soc. 31:3, No. 5, 1956. 5. Cozen, L.: Office Orthopedics, ed. 2, Philadelphia, Lea & Febiger, 1953, pp. 120, 138, 145, 156, 234. 6. Nicolson, W. P., Jr., and Skandalakis, J. E.: Control of postoperative pain, J.M.A. Georgia 46:471, 1957. 7. Piper, C. E., and Nicklas, F. W.: Percodan for pain in industrial practice, Indust. Med. 23:510, 1954; abstracted, Clin. Med. 3:1008, 1956, Current M. Digest 22:135, No. 3, 1955.

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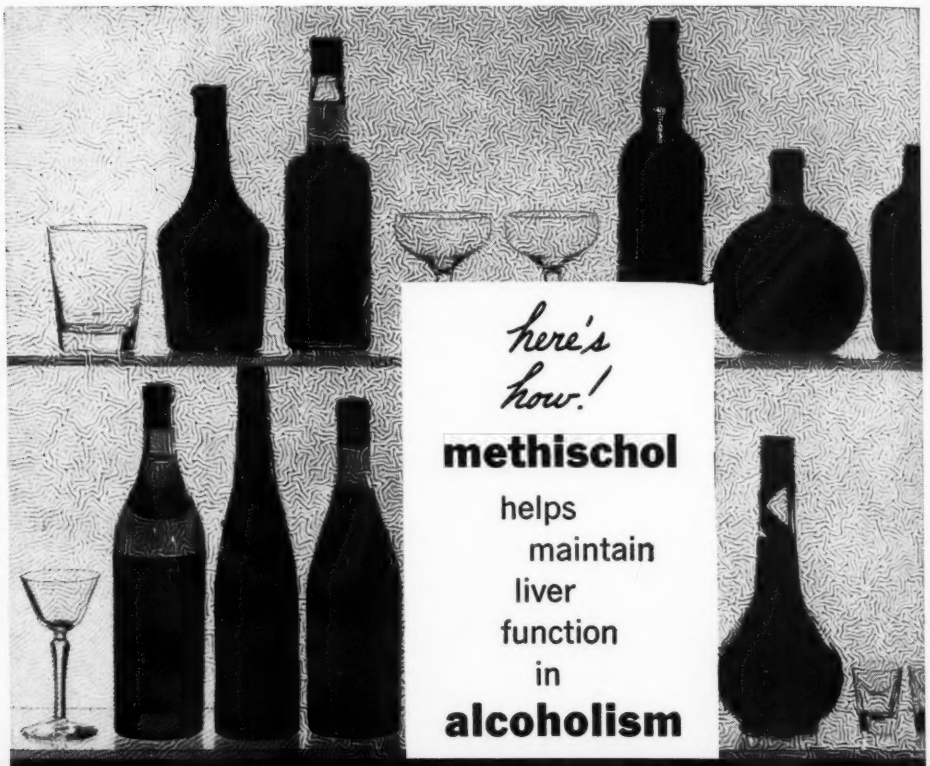

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Methischol, the original, complete lipotropic formula, helps to prevent and reverse liver damage, fatty infiltration of the liver, and cirrhosis in the alcoholic by helping to . . .

- **remove infiltrated fat and thus reduce liver size and tendency to fibrosis**
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- **tends to improve appetite and nutritional state impaired by liver dysfunction**

Prescribe Methischol for every patient threatened by or suffering hepatic damage in . . .
nutritional cirrhosis · alcoholism · hepatitis (toxic) · obesity · diabetes

capsules: bottles of 100, 250, 500 and 1000
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In response to
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from dermatologists

***Winthrop Laboratories
now makes available***

TRIQUIN®

FOR LUPUS ERYTHEMATOSUS AND LIGHT-SENSITIVITY ERUPTIONS

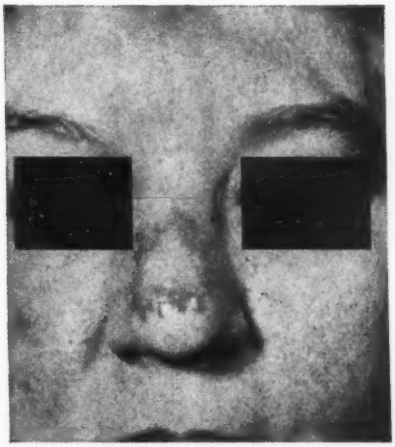
WHAT IT IS:
A combination of Atabrine® hydrochloride 25 mg., Aralen® phosphate 65 mg. and Plaquenil® sulfate 50 mg.

WHAT IT'S FOR:
Treatment of lupus erythematosus (chronic discoid type) and polymorphic light eruptions (light-sensitivity eruptions, solar urticaria or dermatitis).

HOW IT ACTS:
Each of the three components produces beneficial response in lupus erythematosus and light-sensitivity eruptions. Since the dose of each of the Triquin components is very low, overall toxicity is reduced and clinical tolerance improved. Furthermore, the three components appear to act synergistically.

HOW SUPPLIED:
Triquin tablets in bottles of 100, sold on prescription only.

Write for TRIQUIN booklet.



DOSAGE:
Lupus. Average initial adult dose, 1 or 2 tablets after meals and at bedtime. Dosage should be reduced gradually at two week intervals to 1 or 2 daily.

Light-Sensitivity Eruptions. Average initial adult dose, 1 tablet after breakfast and lunch. May be reduced after several weeks to maintenance dosage of 1 tablet daily.

Triquin, Atabrine (brand of quinacrine), Aralen (brand of chloroquine), and Plaquenil (brand of hydroxychloroquine), trademarks reg. U.S. Pat. Off.

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RELOCATION DESIRED—General and Industrial Surgeon desires change in location due to economic deterioration of region. Small clinic or hospital preferred. Willing to do some general practice. Contact HHH c/o SMJ.

Continued from page 936

a Vice-President of the American Psychiatric Association.

Dr. William S. Brumage, Director of the Division of Cancer and Heart Diseases for the State Health Department, Austin, has been elected President of the Texas Public Health Association.

Dr. George Ehni, Professor of Neurological Surgery and head of the Division of Neurological Surgery at Baylor University College of Medicine, Houston, has been chosen President-Elect of the Texas Neuropsychiatric Association.

Dr. A. J. Magliolo, Dickinson, is a member of that town's school board and a member of the executive committee of the Texas Association of School Boards.

Dr. W. M. Greenwood, West Columbia, has been named Brazoria County's 1961 "Doctor of the Year" by the county society's Woman's Auxiliary.

Dr. Dwight E. Curry, Port Arthur, has accepted a position as Chief of the Outpatient Department of the U. S. Public Health Service in Port Arthur.

Dr. Duncan O. Poth, San Antonio, is Vice-President of the Noah Worchester Dermatological Society. He is also the new President of the Texas Dermatological Society.

Dr. Walker A. Lea, Jr., Director of the Department of Dermatology, Scott and White Clinic, Temple, has been elected to the New York Academy of Sciences.

Continued on page 52

After episiotomy

What now?

Chymar,® for one thing

SUPERIOR SYSTEMIC ANTI-INFLAMMATORY ENZYME

to control inflammation, swelling, and pain in EPISIOTOMIES, pelvic inflammatory disease, postpartum breast engorgement, thrombophlebitis.

Chymar reduces inflammation and edema of tissues, hastens absorption of blood extravasates, diminishes pain, and thus promotes smoother healing. More than 80% of episiotomies have shown complete relief of edema in the wound, and in no case was it necessary to release sutures.[1] Chymar also reduces pain and engorgement in the postpartum breast.[2] In pelvic inflammatory disease, Chymar has reduced inflammation, swelling and pain in 85% of patients.[3] And in thrombophlebitis, Chymar rapidly diminishes pain, swelling and tenderness around the vein; allows earlier activity of the patient.[4]

1. Fullgrabe, E. A.: Ann. New York Acad. Sc. 68:192, 1957. 2. Clinical Reports to the Medical Department, Armour Pharmaceutical Company, 1960. 3. Reich, W. J., and Nechtow, M. J.: Am. Pract. & Digest Treat. 11:45, 1960. 4. Teitel, L. H.; Siegel S. J.; Tendler, J.; Reiser, P., and Harris, S. B.: Indust. Med. & Surg. 29:150, 1960.

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Chymar Aqueous and Chymar (in oil) contain crystallized chymotrypsin, a proteolytic enzyme with systemic anti-inflammatory properties. Each cc. of Chymar contains 5000 Armour Units of chymotrypsin, 0.18% methyl paraben, 0.02% propyl paraben, 2% aluminum monostearate, q.s. sesame oil. Each cc. of Chymar Aqueous contains 5000 Armour Units of chymotrypsin, 0.9% sodium chloride, 0.2% calcium acetate, 0.01% thimerosal, q.s. Water for Injection. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac or renal origin; hastens absorption of blood and lymph extravasates; helps to liquefy thick tenacious mucous secretions; restores local circulation; promotes healing; reduces pain. INDICATIONS: Chymar is indicated in respiratory conditions such as asthma, bronchitis, sinusitis and rhinitis; in accidental trauma to speed reduction of hematomas, bruises and contusions; in inflammatory dermatoses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologic conditions therapeutically or in conjunction with antibiotics in pelvic inflammatory disease; in surgical procedures as biopsies, G.I. surgery, hernia repairs, hemorrhoidectomies, plastic surgery and thrombophlebitis; in peptic ulcers and ulcerative colitis as an adjunct to diet, antispasmodics, antacids, etc.; in genitourinary disorders as epididymitis, orchitis and prostatitis; in eye conditions as acute conjunctivitis, traumatic edema, hematomas, and eye surgery, in dental and oral surgery as fractures of the mandible or maxilla, alveolectomies, denture fitting, and multiple extractions; and in obstetrics as in episiotomies, breast engorgement, and thrombophlebitis. PRECAUTIONS: Chymar and Chymar Aqueous are for intramuscular injection only. Although sensitivity to chymotrypsin is uncommon, reactions to anti-inflammatory enzymes have been observed. The usual remedial agents (epinephrine, corticotropin (HP* ACTHAR Gel), antihistamine, aminophylline, etc.) should be readily available in case of untoward reactions. Precautions (scratch testing for Chymar (in oil), scratch or intradermal testing for Chymar Aqueous) should be exercised in those patients with known or suspected allergies or sensitivities. As with any foreign protein, patients may develop sensitivity from repeated injections. It is, therefore, recommended that the above precautions be considered prior to administration. In further treatment of those patients in whom a previous injection of chymotrypsin produced signs of possible sensitivity, such as localized edema and erythema at injection site, urticaria, conjunctivitis, etc., particular care must be exercised. INCOMPATIBILITIES: With usual agents, none known—e.g., compatible with antibiotics and anesthetics. DOSAGE: 0.5 cc. to 1.0 cc. deep intramuscularly once or twice daily, depending on severity of condition. Decrease frequency as course of condition is altered. In chronic or recurrent conditions, 0.5 cc. to 1.0 cc. once or twice weekly. SUPPLIED: Chymar in Oil 5 cc. vials and Chymar Aqueous 1 and 5 cc. vials; 5000 Armour Units of proteolytic activity per cc. *Highly Purified.

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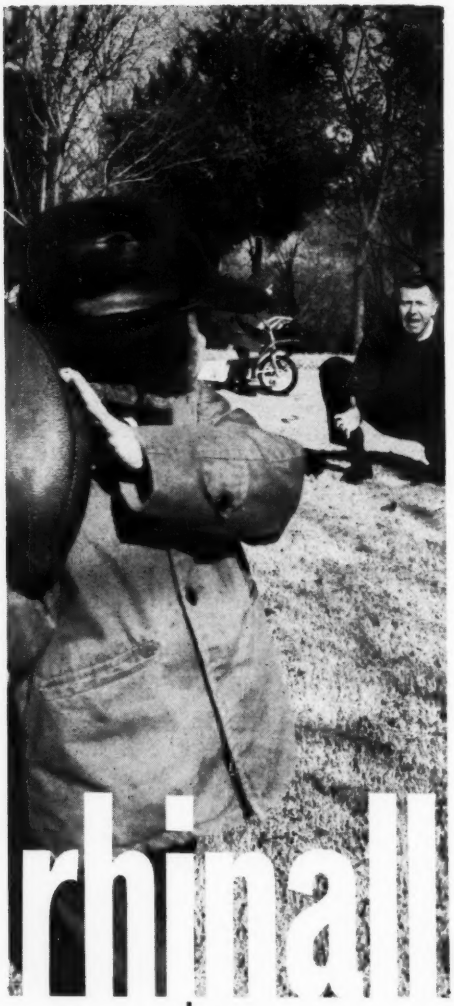

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- Small dosage—well tolerated
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'Propadrine' Hydrochloride 0.3%
In an Isotonic Saline Menstruum.

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Continued from page 50

Dr. B. Randol Hardwick has been elected President of the Rotary Club of Western Fort Worth.

Dr. Leonard J. Flohr, Dallas, is a new Fellow of the American College of Physicians.

Dr. Chester C. Shotts, San Antonio, has been elected President of the Alamo Heights High School Board of Directors. Another San Antonio surgeon, Dr. M. B. Oxford, is a member of the Board.

County medical societies in Texas have announced the following officers for 1961: *Travis,* Dr. Morris D. McCauley, President; Dr. Ruth M. Bain, President-Elect; and Dr. Albert F. Vickers, Secretary-Treasurer, all of Austin; *Upshur,* Dr. J. L. Fenlaw, President; and Dr. Madison S. Ragland, Secretary, both of Gilmer; and *Falls,* Dr. Roy G. Giles, President; Dr. Sidney W. Hughes, Vice-President; and Dr. Howard Lee Smith, Secretary-Treasurer, all of Marlin.

VIRGINIA

The Roanoke Academy of Medicine has established the Roanoke Academy of Medicine Foundation to sponsor and encourage the advancement of the science of medicine, and to establish and maintain a medical library for the benefit of members of the Roanoke Academy of Medicine and other physicians. The Foundation is chartered to permit reception of Federal income tax deductible gifts, and a Memorial Program is now functioning. The officers are: Dr. Alexander McCausland, President; Dr. John A. Martin, Secretary; and Dr. Harry B. Stone, Jr., Treasurer, all of Roanoke.

Officers of the Neuro-Psychiatric Society of Virginia are: Dr. Robert H. Thrasher, Norfolk, President; Dr. Howard H. Ashbury, Williamsburg, President-Elect; and Dr. Edward W. Gamble II, Radford, Secretary-Treasurer.

The Medical Society of Virginia has the following new members: Drs. Thomas G. McWilliams and John R. Wadleigh, both of Arlington; Dr. Albert F. Borges, Falls Church; Dr. Robert A. G. Jones, Hampton; Drs. Edward L. Alexander, Jr., and Italo P. Rinaldi, both of Newport News; Dr. Jerome E. Adamson, Norfolk; Drs. William T. Clarke, John H. Greig, and Walter H. Mendel, all of Richmond; Dr. Carold Jean Whidden, Rural Retreat; Drs. Emilio Espinosa, Donald S. Howell, and William A. Seawell, all of Suffolk; and Dr. Bahri O. Gungor, Vienna.

Dr. Paul D. Camp, Richmond, has been elected one of the 24 members of the Council of Directors of the Inter-American Society of Cardiology.

Dr. F. Preston Titus, Alexandria, has been elected President of the Board of Trustees of the Alexandria Community Health Center.

Dr. Victor P. Owen, Jarratt, has been named Director of the Brunswick-Greenville-Mecklenburg Health District.

WEST VIRGINIA

Dr. Harold G. Young has been appointed a Clinical Associate Professor of Surgery at West Virginia University.

Dr. Clyde Litton, Charleston, is President of the Ohio Valley Plastic Surgery Society.

Continued on page 54

For the irritable G.I. tract

Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES

MILPATH-400—Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.
Bottle of 50.
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For full details contact:

DIRECTOR

Fifth U. S. Civil Service Regional Office,
275 Peachtree, N.E., Atlanta 3, Georgia.

Continued from page 52

Dr. Glenn Frederick Van Winkle has accepted an appointment as a member of the medical department of Union Carbide Chemical Company in South Charleston.

Dr. Milford L. Hobbs, who has served as Chairman of the Department of Pathology at the West Virginia University School of Medicine since 1947, has resigned to accept a position as Chief Pathologist and Director of Laboratories at St. Mary's Hospital in Huntington.

Officers of the West Virginia Chapter of the American College of Surgeons are: Dr. Victor S. Skaff, Charleston, President; Dr. Francis L. Coffey, Huntington, Vice-President; and Dr. Jack C. Morgan, Fairmont, Secretary Treasurer.

Dr. Robert A. McDougal, Parkersburg, is President of the West Virginia Association of Blood Banks. Dr. Charles W. Thacker, Parkersburg, is President-Elect.

Dr. Edwin B. Whitemore, Jr., Marion, Virginia, has been appointed Superintendent of Huntington State Hospital in Huntington.

Officers of the Harrison County Medical Society include Dr. Harry T. Linger, President; Dr. Andrew J. Weaver, President-Elect; Dr. A. Robert Marks, Secretary; and Dr. Robert S. Wilson, Treasurer, all of Clarksburg.

Dr. William J. Steger is President of the Ohio County Medical Society. Dr. Charles H. Hiles is President-Elect; Dr. H. G. Dickie, Jr., Secretary; and Dr. David W. Palmer, Treasurer. The physicians are all of Wheeling.

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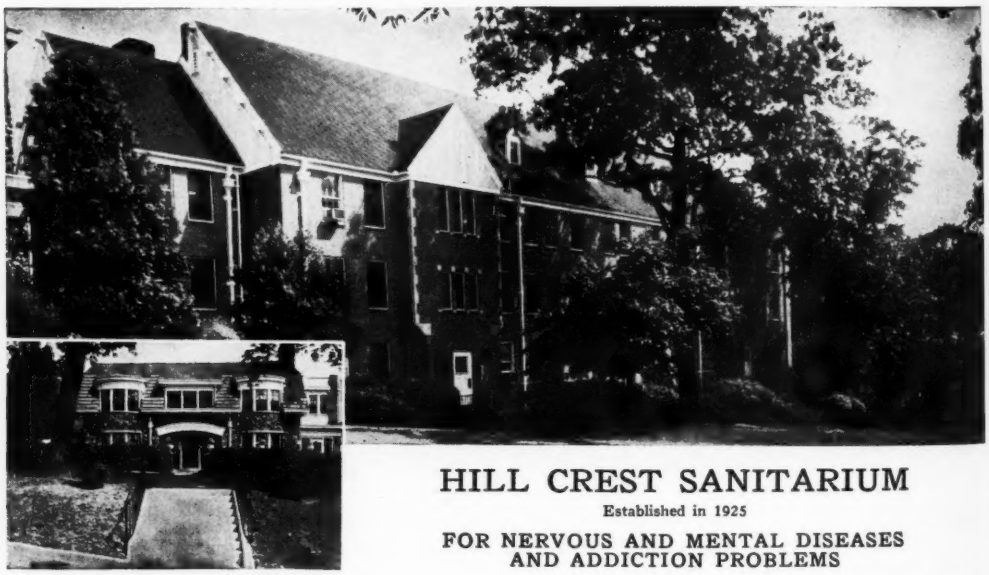

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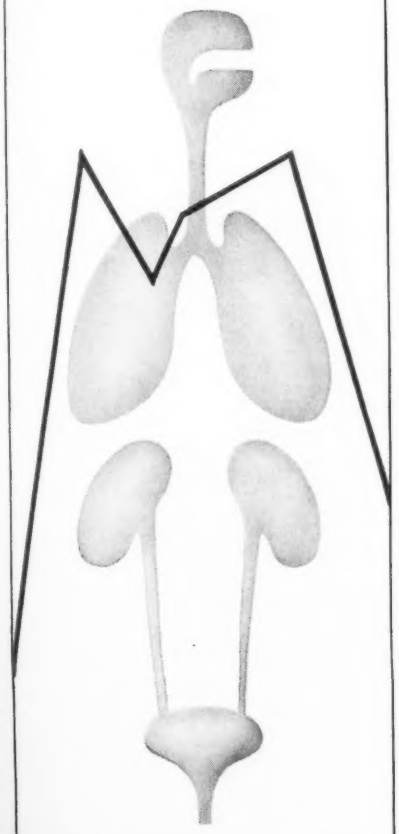

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High blood levels produce antibacterial activity in deep tissue at the focus of infections. SULFOSE contains three independently soluble sulfonamides to help protect against crystalluria.

- SULFOSE is especially effective in urinary tract and upper respiratory infections
- Bacteria resistant to antibiotics may respond to SULFOSE
- SULFOSE causes fewer complications such as diarrhea, gastric upset, superinfections
- SULFOSE permits reserving the antibiotics for severe, fulminating infections
- SULFOSE is economical

SUSPENSION TABLETS

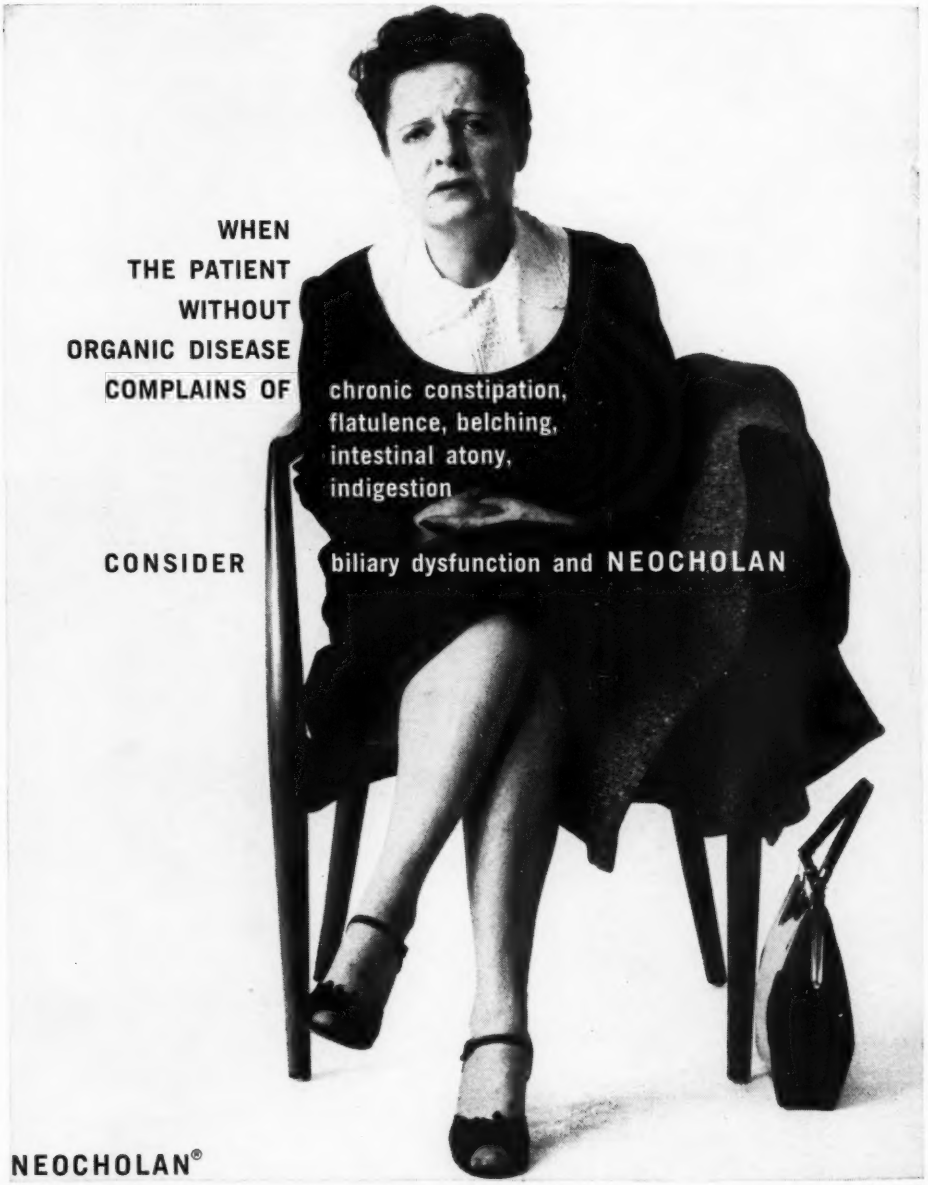
SULFOSE®

Triple Sulfonamides, Wyeth
(Trisulfapyridimines: Sulfadiazine, Sulfamerazine, Sulfamethazine)

Wyeth® SERVICE TO MEDICINE

For further information on limitations, administration, and prescribing of SULFOSE, see descriptive literature or current Direction Circular.

Wyeth Laboratories Philadelphia 1, Pa.



NEOCHOLAN®

Your patient will often respond promptly to Neocholan therapy. It greatly increases the flow of thin, nonviscid bile and corrects biliary stasis by flushing the biliary system. It also relaxes intestinal spasm, resulting in an unimpeded flow of bile and pancreatic juice into the small intestine. Neocholan helps to promote proper digestion and absorption of nutrients. It also encourages normal peristalsis by restoring intestinal tone.

Each tablet provides: Dehydrocholic Acid Compound, P-M Co. 265 mg. (Dehydrocholic Acid, 250 mg.); Homatropine methylbromide 1.2 mg.; Phenobarbital 8.0 mg. Supplied in bottles of 100 tablets.

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DIVISION OF THE DOW CHEMICAL COMPANY
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ENDS ITCH FAST

ORAL ALLERCUR REACHES THE SKIN IN 10 MINUTES[1] FOR PROLONGED RELIEF

Allercur is the systemic answer to a dermatology problem. This single agent provides fast, prolonged relief of itching, both allergic and nonallergic, with only 2 to 4 tablets daily —without timed-release devices. Drowsiness and other side effects are of low degree. Unlike topical preparations, Allercur frees the patient of messy, inconvenient local application. Many risks of systemic phenothiazine and glucocorticoid therapy are decreased.

Effective: "An excellent or good antipruritic response occurred in 69 patients (79.5%). No toxic reactions occurred and there were virtually no side effects. Particularly notable were the absence of drowsiness and the rapidity with which the remission of itching occurred."[2] Allercur is also effective in the management of conditions such as nasal allergy, including seasonal hay fever.

CAUTION: If drowsiness occurs, patients should avoid activities demanding alertness.

AVERAGE DOSE: 2 to 4 tablets daily in divided doses.

SUPPLIED: Tan, scored tablets, each containing 20 mg. clemizole HCl, in bottles of 100.

REFERENCES: 1. Kimmig, J.: Hautarzt 3:414 (Sept.) 1952. 2. Butler, P.G.: Western Med. 1:16 (Nov.) 1960. Bibliography on request.

Rx PFERIG

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

when allergies occur Rx

ALLERCUR*

*Reg. T.M., Schering, A. G., Berlin

(clemizole HCl)

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in allergies *For smooth, continuous control of allergic symptoms—relief in minutes for hours, with virtually no side-effects. And there is a dosage form for every allergic patient.*

Pulvules® • Suspension • Pediatric Pulvules **Co-Pyronil®**

(Pyrrobutamine compound, Lilly)

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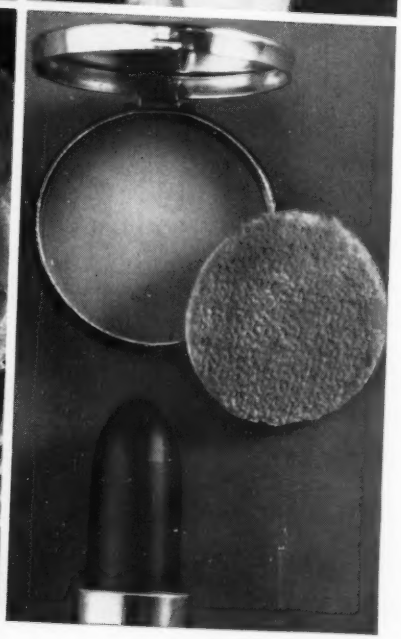


PINWORMS?

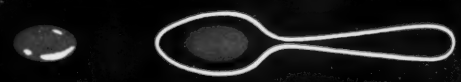
Povan SINGULARLY EFFECTIVE IN A SINGLE DOSE

(pyrvinium pamoate, Parke-Davis)

POVAN provides a simplified and clinically proved means of bringing a common medical problem under control. Through its unusual ability to clear most cases of pinworm infection with just one dose, POVAN permits this problem to be dealt with in a practical manner...preferably on a family or institution-wide basis.

POVAN is well tolerated...readily accepted in both dosage forms...and not appreciably absorbed through the gastrointestinal tract. Its single-dose efficacy makes therapy not only convenient, but economical as well.

Supplied: POVAN is available in suspension or tablet form. The pleasant-tasting, strawberry-flavored suspension is supplied in 2-oz. bottles and the tablets in bottles of 25.



The suspension contains pyrvinium pamoate equivalent to 10 mg. pyrvinium base per cc. The sugar-coated tablets each contain pyrvinium pamoate equivalent to 50 mg. pyrvinium base. *Dosage:* Children and adults, a single oral dose equivalent to 5 mg. per Kg. of body weight. *Precautions:* Infrequent nausea and vomiting and intestinal complaints have been reported. Tablets should be swallowed whole to avoid staining teeth. Will color stools a bright red. Suspension will stain most materials.

PARKE-DAVIS

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